

REPORT OF THE  
National Institutes  
of Health:  
Opportunities for  
Research on  
Women's Health

September 4-6, 1991  
Hunt Valley, Maryland

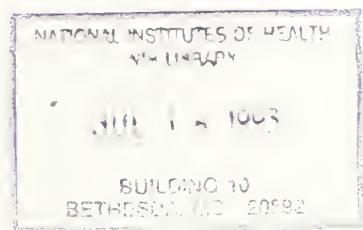
Office of Research on Women's Health  
Office of the Director  
National Institutes of Health



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With a Foreword  
by Dr. Bernadine Healy,  
Director of the National Institutes of Health





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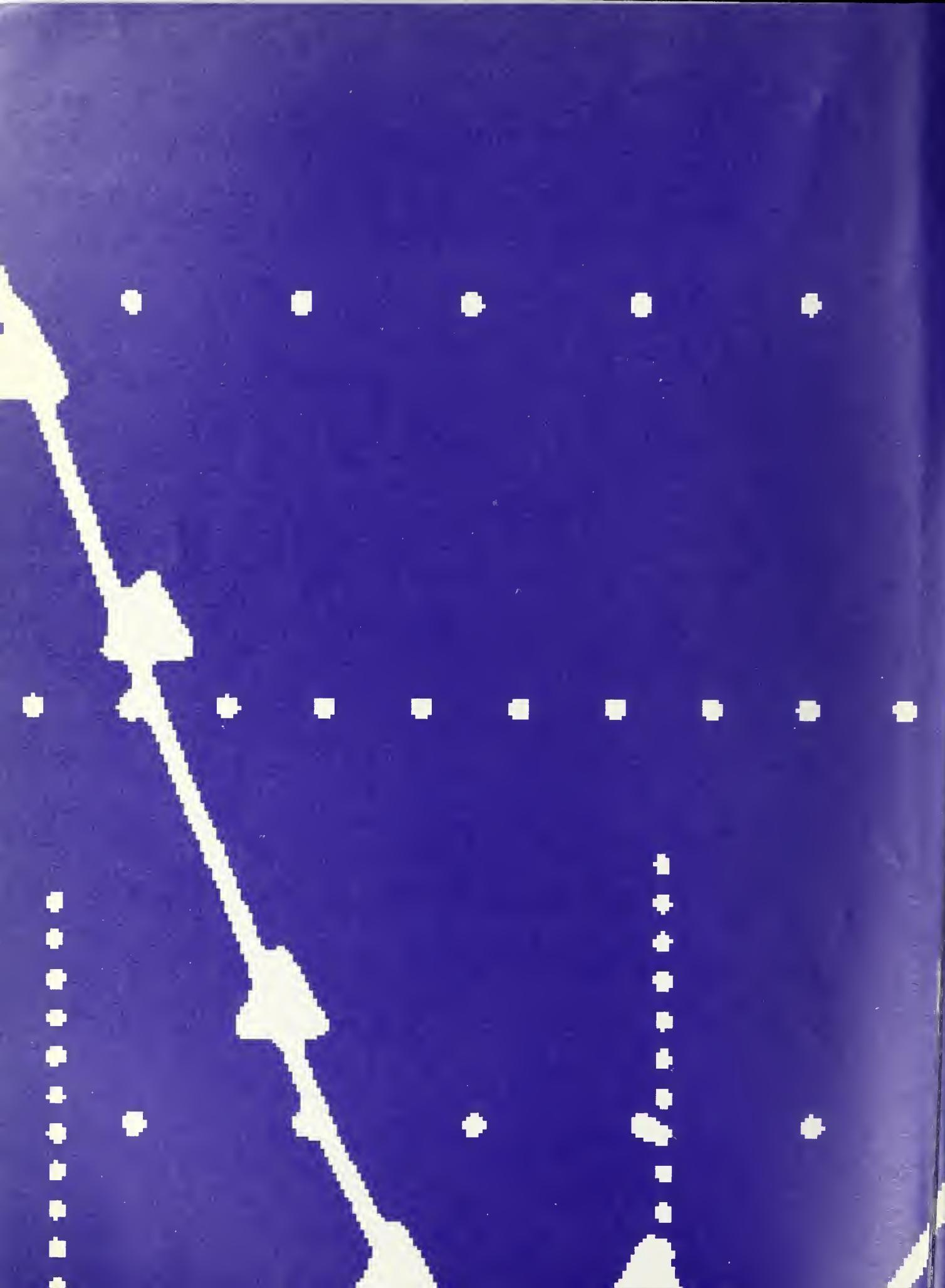
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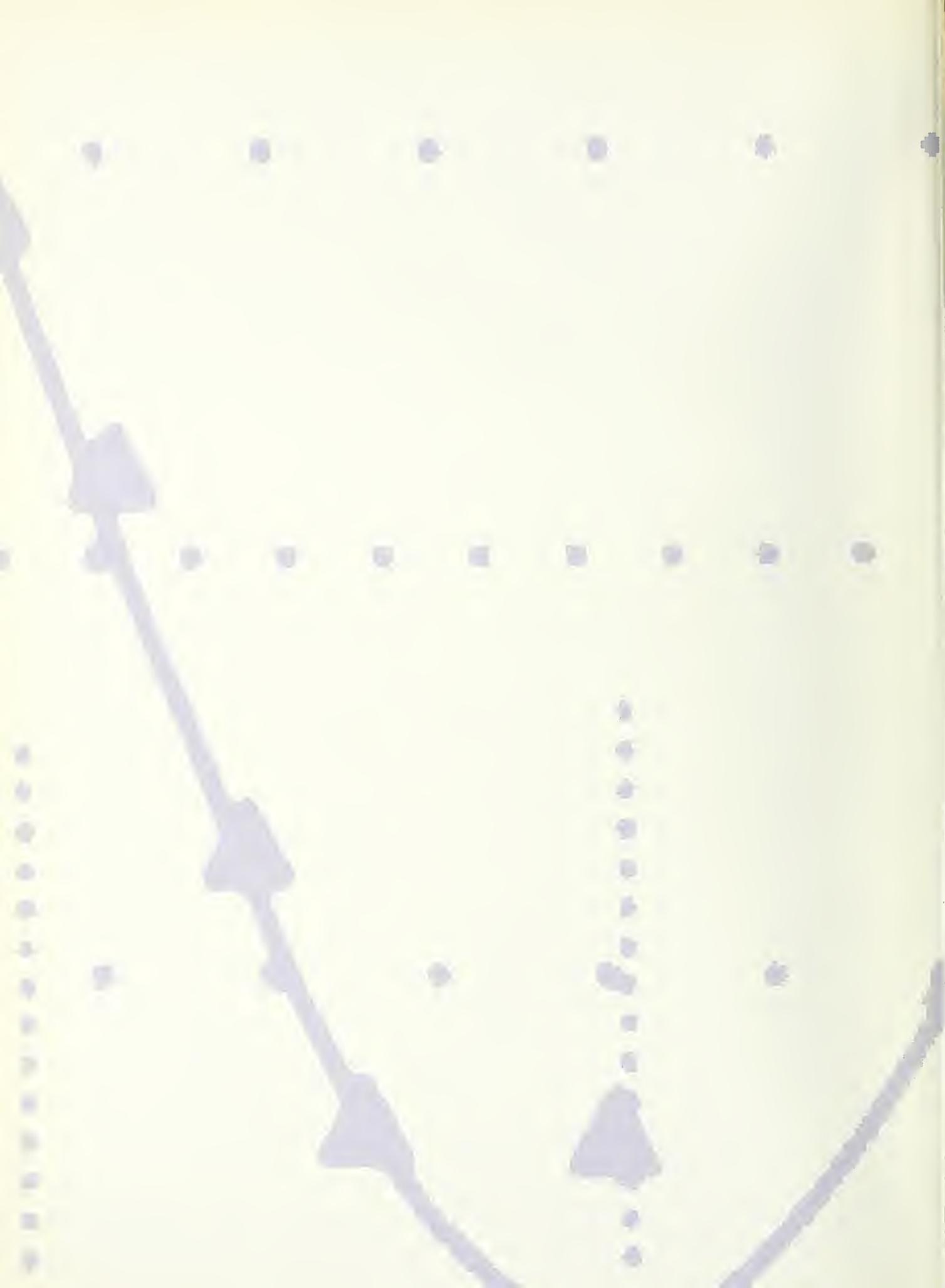
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# PART ONE



# FOREWORD

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# FOREWORD

*Bernadine Healy, M.D.,  
Director,  
National Institutes of Health*

In recent years, Americans have experienced an awakening about the importance of women's health: the importance of good health not only to women themselves but to our society as a whole. This awakening has been spearheaded by advocacy groups and members of Congress, who have called for more research into the causes, treatments, and prevention of diseases that rob women of their health. The National Institutes of Health (NIH), the Federal agency charged with extending healthy life and reducing the burdens of illness and disability for all Americans through scientific research, has heard this call and responded with an awakening of its own.

In 1990 the NIH established, within the Office of the Director, the Office of Research on Women's Health (ORWH), headed by Dr. Vivian Pinn. Among other activities designed to promote women's health, the ORWH is charged with ensuring that all clinical trials supported by the NIH include adequate numbers of women. Over the past year, the ORWH has convened two major conferences on opportunities in women's health research and opportunities for women in biomedical careers. This report is the result of that first conference, held in September of 1991.

This report sets forth an agenda for national research efforts in women's health. In crafting the agenda, workshop participants focused on the end point of NIH's efforts: improved health for all women, regardless of their race, socioeconomic status, or age. As Director of the NIH, let me point out that the underlying principle of NIH's efforts in women's health research is fundamental to the overall mission of the NIH and is best expressed in our motto, "Science to extend healthy life"—the life of each and every citizen, whether male or female.

The NIH has placed women's health high on its research agenda. To gain a comprehensive view of NIH's efforts in women's health research, it is essential to understand these efforts not just within the context of the NIH, the world's largest supporter of biomedical research, but within an historical context as well.

## **Historical Context of the Awakening**

Throughout history, women have generally been viewed as inferior to men. Although differences between the sexes were readily acknowledged, the characteristics attributed to women were not always laudable or even biologically correct. Not surprisingly, these social attitudes influenced the

medical community's treatment of women patients. For example, as recently as the 1960s, faculty at our Nation's leading medical schools taught future physicians that all women should have their children between the ages of 18 and 25. Illnesses that women developed in their 30s and 40s, such as endometriosis, were seen as punishment for delaying or not having children. Needless to say, this medical judgment owed more to prevailing social attitudes than to science.

The same social attitudes influenced the selection of study populations in biomedical research. As late as the 1980s, a major study on the preventive effects of aspirin in treating coronary disease involved some 22,000 men, but not a single woman. Another study looked at the role of estrogen in preventing heart disease, but only in men.

Such studies have suffered from the underlying assumption that men are the normative standard, and such studies have served to reinforce the myth that heart disease is unique to men. I refer to this practice as the Yentl syndrome.<sup>1</sup> The fact is that heart disease has long been the leading cause of death for women in the United States. Clearly, by the 1990s it was time for medical researchers to wake up to this fact, and for taxpayer-supported research to reflect the fact that women pay taxes, too.

## Closing the Knowledge Gaps for a More Integrated View of Health

Shortly after becoming Director of the NIH in 1991, I committed the agency to a program aimed at closing the startling gaps that still exist in our knowledge of women's health. The Women's Health Initiative, a 14-year \$625 million effort, will study some 150,000 women at 45 clinical centers across the United States and will be the largest clinical study ever undertaken in this country on the health of either men or women. The study's protocol is described by the director of the Women's Health Initiative, Dr. William Harlan, in Appendix 1 of this report.

The initiative has two closely related goals. The first of these is to decrease the prevalence of cardiovascular disease, cancer (especially breast can-

cer), and osteoporosis among women. The initiative will develop recommendations on diet, hormone replacement therapy, diet supplements, and exercise: practical information that can be used by physicians and by women of all ethnic groups and socioeconomic classes. The second, related goal is to evaluate the effectiveness of various strategies for motivating older women to adopt health-enhancing behaviors.

With its emphasis on the relationship between behavior and health, the Women's Health Initiative is particularly timely. Congress recently acted to bring the research components of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) into the NIH. This merger will allow for increased collaboration in NIH's efforts to promote a more integrated view of women's health. As described in this report, addictions and depression exact a tremendous toll on women in our society, while diet, smoking, exercise, and other behaviors obviously have a major influence on health. This report also notes that, in 1990, the highest proportional increase in AIDS occurred among women, making AIDS the leading cause of death among women ages 15 to 49 in several American cities. The Women's Health Initiative and new integration of NIH and ADAMHA will yield valuable information on the best ways to encourage women to change their behavior to preserve good health.

The Women's Health Initiative, which will begin shortly after the release of this report, has received strong endorsement from individuals and groups nationwide. Congress has generously provided sufficient funding for the first year of the study, and in addition to congressional support, there has been overwhelming support and offers of assistance from physicians, their patients and patients' families, laboratories, universities, and individual researchers. One outside organization even offered to donate funding. Media coverage of the initiative has also been gratifyingly extensive.

The NIH launched the Women's Health Initiative with full recognition of the fact that closing the vast knowledge gaps pertaining to the health of

women requires a commitment from all the Institutes and Centers of the NIH. The leaders of the Institutes and Centers have responded to the initiative with great enthusiasm and have selected women's health as one of the areas of research to be given special emphasis in the NIH's new strategic plan, which will be released in the fall of 1992.

In addition to providing women with practical information on how to preserve their health, the Women's Health Initiative will provide the scientific community with valuable knowledge on the design and implementation of future clinical studies. Because the initiative will recruit women across geographic, racial, ethnic, and socioeconomic lines, it will yield a wealth of information on how best to recruit and retain women participants in clinical trials. Such information will be particularly useful in helping researchers work with segments of our society that have not previously been included in most biomedical research.

## **Women: Filling the Gaps in Leadership**

In the 1960s, men outnumbered women in college by a ratio of almost two to one. Today, there are approximately one million more women than men studying in colleges and universities; more important, it is projected that by the year 2000, more women than men will be earning doctorate degrees. Entrants to medical school reflect the same national trend: during the past 5 years, the number of men going to medical school has fallen by more than 9 percent while the number of women has increased by the same percentage. (See my editorial, "Women in Science: from Panes to Ceiling."<sup>2</sup>) Enrollment of Black women has increased by 23 percent and Asian women by more than 100 percent. In fact, were it not for this trend in women offsetting falling male enrollment, our Nation could face a brainpower shortage in medicine and biomedical research at a time when the complex nature of science demands the energies and resources of a diverse talent base.

The national trends in education hold great promise for research on women's health. There can be no question that an agenda for women's health research would be enhanced and gender and eth-

nic disparities in medical treatment and research reduced not only by increasing the numbers of women and minorities in medicine, but also by encouraging them to seek leadership positions in teaching, research, and the practice of medicine.

Unfortunately, throughout their academic and professional careers, women researchers receive more negative treatment than their male counterparts, as documented by Jonathan Cole in his recent book, *The Outer Circle: Women in the Scientific Community*. Cole describes what he refers to as positive and negative kinetic reactions or "kicks" that occur at every stage in a career. Overall, he found that women in science experience far too few positive kicks, that is, the rewards and recognition that build the self-confidence needed to conduct research and seek positions of leadership.

In an effort to provide a positive kick for women in biomedical careers, the ORWH sponsored a workshop last June that brought together 450 women and men ranging from high school students to senior executives and leaders in science and politics to discuss how, on a national scale, we can encourage, maintain, and promote women in scientific and medical careers. Just as the awakening about research on women's health did not gain national momentum until a number of women leaders in and outside of Congress took their view to the American people, so the NIH, through the ORWH, is taking the lead in fostering awareness about the need to increase opportunities for women and minorities in biomedical careers. Recommendations from the workshop, *Women in Biomedical Careers: Dynamics of Change, Strategies for the 21st Century*, will be published early in 1993.

Through the ORWH and the Women's Health Initiative, the NIH is making good on our commitment to helping all of the people of the United States enjoy better health. But we need the help of the biomedical community to achieve our goals. We hope that this report will serve as a call to arms for medical researchers nationwide to pursue neglected topics in women's health research. Each gap in knowledge that it describes can be

read as an invitation to fill that gap. Each health crisis that it describes is a call for researchers and practitioners to alleviate that crisis. Each recommendation is a challenge for leaders of the biomedical research community to inspire others to action.

Political pundits have referred to 1992 as the year when women began to make a difference at the polls. In the future, I hope that many in the biomedical community will remember 1992 as the

year that they heeded NIH's call to arms and began to make a difference in women's health.

## **References**

1. Healy, B. "The Yentl Syndrome," *New England Journal of Medicine* 325:274-276 (1991).
2. Healy, B. "Women in Science: from Panes to Ceiling," *Science* 255:1333 (1992).

## PREFACE

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# PREFACE

Vivian W. Pinn, M.D.,  
Director,  
*Office of Research on  
Women's Health*

The Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH) was established in September 1990 as part of a vigorous and ongoing effort to strengthen and enhance research related to diseases, disorders, and conditions that affect women and to ensure that women are appropriately represented in biomedical and biobehavioral research studies. Dr. Ruth Kirschstein was appointed Acting Director of this new office.

Initiating actions to achieve this mandate, the ORWH sponsored two critical activities: a public hearing and a workshop, Opportunities for Research on Women's Health. The public hearing, held in June 1991, afforded the opportunity for representatives of over 90 organizations interested in women's health to shape the direction of the workshop and, ultimately, the ORWH Research Agenda on Women's Health. The final results of that workshop—convened in Hunt Valley, Maryland, in September 1991—are presented here.

Under Dr. Kirschstein's leadership, and in collaboration with the Task Force on Opportunities for Research on Women's Health, the workshop

developed into a multidisciplinary effort focused on biomedical and biobehavioral issues germane to women's health across the life span.

Part One of this report is designed for the lay public and for those seeking an overview and highlights of the scientific reports developed at the workshop. In her *Foreword*, Dr. Bernadine Healy, Director of NIH, explains women's health research as integral to the mission of the NIH and describes the historical context of the recent awakening of our Nation to the issues of women's health. In her *Introduction*, Dr. Kirschstein places the development of the workshop in the context of the mission of the Office of Research on Women's Health and highlights the events of the past decade that led to the current emphasis on the issues relevant to women's health. The *Executive Summary* is a synopsis of the papers and working group reports which constitute Part Two of this document. For each report, the synopsis highlights the principal issues identified by the working group, and converts their highly technical recommendations for research into the form of general research questions underlying the recommendations.

Part Two of this report presents (a) the background papers on morbidity and mortality in women, the issue of women as research subjects, and women's careers in biomedical sciences, and (b) the full texts of the reports of the 10 working groups. An *Overview* by the workshop cochairs, Drs. William R. Hazzard and Mary Lake Polan, introduces the major themes and issues treated by each working group. Drs. Hazzard and Polan provided leadership throughout the planning and implementation phases of the workshop. Quotations from public hearing and workshop participants are interspersed throughout the text to highlight the concerns expressed in the public testimony and the responses of the workshop to those concerns.

This report represents an agenda for the NIH to utilize in addressing the gaps in knowledge about women's health through enhancing and implementing biomedical and biobehavioral research during the next decade. This is the challenge that we face as we launch women's health into the 21st century. We invite and urge you to join us in this exciting and exhilarating challenge, for we must unify our collective expertise, abilities, wisdom, and spirit in this quest for knowledge about women's health if we are to succeed.

Vivian W. Pinn, M.D.

# INTRODUCTION

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# INTRODUCTION

*Based on remarks by  
Ruth L. Kirschstein, M.D., Director, National  
Institute of General Medical Sciences and  
Former Acting Director, Office of Research on  
Women's Health*

In 1983, the Assistant Secretary for Health established a Public Health Service Task Force on Women's Health Issues. One of its principal accomplishments was the preparation of a two-volume report, *Women's Health: Report of the Public Health Service Task Force on Women's Health Issues*. The first part of this report was published in the January/February 1985 issue of *Public Health Reports*; volume II was issued as a separate publication from the Department of Health and Human Services in October 1987. The report discussed a broad array of women's health issues across the life stages, particularly in the context of the sociological changes in the United States taking place in the latter years of the 20th century. One of the most important recommendations in the task force report was that "biomedical and behavioral research should be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in, women in all age groups."

Since that time, the issue of women's health, in a political, social, and biomedical sense, has come a long way. Among the most significant milestones was the creation of a new Office of Research on

Women's Health (ORWH) within the Office of the Director of the National Institutes of Health (NIH) in September 1990. The mandate of this new office has been to strengthen and enhance the prevention, diagnosis, and treatment of illness in women and to enhance research related to diseases and conditions that affect women.

As part of its overall mandate, the ORWH has been charged with three critical objectives. The first is to ensure that, in the performance of any research supported by the NIH, the important issues that pertain to women's health are adequately addressed. These relate to diseases, disorders, and conditions that are unique to, more prevalent among, or far more serious in women, or for which there are different risk factors or interventions for women than for men.

The second objective is to ensure appropriate participation of women in clinical research, particularly in clinical trials.

The third key objective is to foster the increased enrollment of women in biomedical research—especially in pivotal decision-making roles within both clinical medicine and the research environment.

## Towards Achieving the Objectives

Major steps have been taken at the NIH during the last year toward realizing these objectives. For example, to ensure that women are included in study populations according to the stipulations set forth as its formal policy, the NIH published an expanded Policy Notice in the August 24, 1990, *NIH Guide to Grants and Contracts*, which more fully explains the policy as well as plans for implementation, and also issued an *Instruction and Information Memorandum* to all staff regarding this policy. Within the ORWH, a data-based tracking system has been developed to monitor the enrollment of women in clinical trials and epidemiologic studies. The NIH has stated that, starting with the February 1991 reviews for scientific merit, no Public Health Service grant applications will be accepted unless women are adequately represented in planned clinical research, except in instances for which compelling justification can be provided.

To help answer broader questions, the ORWH arranged with the Institute of Medicine to provide assistance in addressing the legal and ethical barriers to including women in clinical studies. Among several pressing questions pertaining to this issue is whether or not it is possible to overcome the problems related to potential fetal damage, safety in using therapeutic drugs in women of childbearing age, and liability when such women are included in clinical research.

To address the issues of recruiting and promoting women in scientific and medical careers, the ORWH initiated a series of activities during 1992 that included the sponsorship of a major conference on careers and career development for women in biomedical science. The ORWH also is providing support to the Committee on Women in Science and Engineering of the National Academy of Sciences, which is developing a program to achieve greater participation of women in science.

Further, the ORWH functions as a catalyst and a facilitator in enhancing research on women's health by providing supplemental funds to other NIH components to augment new research initiatives or

expand current studies in order to address high-priority areas regarding the health of women.

As one of its most important activities in 1991, the ORWH established an NIH Task Force on Opportunities for Research on Women's Health. The charge to this task force has been to assess the current status of research on women's health, identify scientific research opportunities and gaps in knowledge, and recommend a comprehensive trans-NIH plan for future directions in research on the health of America's women. The principal objective of the task force is to devise a research agenda that will guide the direction of, as well as the funding priorities regarding, research on the health of women throughout the next decade. During the year, the task force held a number of meetings. An important goal of the meetings was to solicit the widest possible scope of opinion regarding the research agenda both from within the NIH and from the external scientific and lay communities.

## Public Hearings

### *June 12 and 13, 1991*

To collect comprehensive information on the current needs in women's research and gain perspective on the full spectrum of those needs, the ORWH held a public hearing on June 12 and 13, 1991, during which advocates for women's health and representatives of scientific and medical organizations were given an opportunity to provide input into the research agenda and the plans for the scientific workshop.

An announcement in the March 22, 1991, *Federal Register* solicited both oral and written testimony from experts speaking for the many groups that address issues pertaining to research in women's health. Representatives from more than 60 organizations across the country came to the NIH to present their statements; more than 40 others submitted written testimony for the record.

A large portion of that testimony emphasized the need to accord priorities to cancer prevention (especially breast cancer), cardiovascular disease, and osteoporosis. Considerable concern was expressed also about autoimmune diseases that affect women in particular. Witnesses and task

force members alike noted the problems that may result from excluding women from clinical trials. Several of those who testified mentioned the current lack of knowledge regarding the complex hormonal cycles of women and, in particular, how these changes may affect absorption, disposition, action, and elimination of drugs. Witnesses also recommended that there be new research initiatives on sexually transmitted diseases (STDs), work site safety, domestic violence, AIDS, and pre- and postnatal care—with a focus on the health of the mother. Other witnesses emphasized the need to develop effective prevention strategies, especially in the areas of bone disorders. A number of individuals commented on the lack of behavioral research as well as the dearth of data on the health of Black and Hispanic women—with an emphasis on the socioeconomic factors that underlie many prevalent health problems.

## **Workshop on Opportunities for Research on Women's Health**

The contributions, commitment, and specific recommendations of those who presented testimony provided important guidance toward planning the Workshop on Opportunities for Research on Women's Health, and also helped to determine many of the particular scientific areas addressed in the course of the 3-day workshop held in Hunt Valley, Maryland, September 4-6, 1991.

Participants at the workshop included experts in the fields of basic and clinical sciences, practitioners interested in women's health, and representatives of women's organizations.

The purpose of the workshop was to arrive at specific, workable recommendations regarding research activities on behalf of all the women in the United States, after consideration of the broadest possible range of issues. To achieve this purpose, the workshop utilized a unique design. According to this design, participants were assigned to working group sessions in two major areas: (1) the major divisions of a woman's life span and (2) the scientific issues, diseases, and impairments that might affect her health and well-being during that life span.

Participants who addressed the Life Span area set the stage for the deliberations of the Crosscutting Science Working Groups by providing a broad perspective regarding the concerns that are intrinsic to every woman during each segment of her life from birth to death. Group discussions were divided into Birth to Young Adulthood, Young Adulthood to the Perimenopausal Years, Perimenopausal to Mature Years, and Mature Years. For the second area, Crosscutting Science working groups addressed the following topics: Reproductive Biology, Early Developmental Biology, Aging Processes, Cardiovascular Function and Disease, Malignancy, and Immune Function and Infectious Diseases. The working groups assessed the current status of women's health, identified research opportunities and gaps in research, and recommended approaches and options for taking advantage of the most promising of these opportunities.

The workshop participants have thereby established a foundation for an NIH-wide research agenda to attain significant progress against the diseases and disorders that place a particular burden on women. This research agenda, which will guide planning efforts at the NIH for the next several decades, is critical to improving the quality of life for all the Nation's women.

Because the workshop was sponsored by the NIH, the primary focus of the working groups' efforts was on the biomedical aspect of the issues. Nonetheless, in their discussions, participants recognized the importance of considering the socioeconomic, legal, and ethical issues that impinge upon health and disease.

## ***Scope of This Report***

This report sets forth the research recommendations developed by the working groups in both the Life Span and Crosscutting Science areas. Each working group's report addresses:

- Key issues (including morbidity and mortality data for the most important diseases and disorders within its parameters)

- Gaps in knowledge for which research is needed
- Major scientific findings of current relevance for future research
- Specific research recommendations.

The issues that bear upon biomedical research on women's health are inextricably linked to two of the principal objectives of the ORWH: ensuring appropriate participation of women in clinical research, especially clinical trials, and increasing the numbers of women in biomedical research careers. The workshop therefore included several formal presentations and considerable discussion on these issues. Highlights from these presentations and related public commentary are also included in this report.

## ***A Comprehensive Effort***

An overarching principle, guiding all the efforts of the ORWH, is the conviction that biomedical research must be targeted to all of America's

women, of all races, all ages, and all socioeconomic and ethnic groups. Further, while the NIH can address only one part of the research puzzle, the ORWH recognizes that research needs do not exist in isolation; they are tied inextricably to other critical issues such as access to health care and insurance coverage. Finally, the ORWH also realizes that researchers must make more intensive efforts to address the health needs of the whole woman, interweaving both medical and behavioral issues—the body and the mind.

Closing the gaps in knowledge regarding women's health may take several years of intensive effort. Those who are impatient for results with immediate clinical applicability may experience difficulty understanding this. However, by adhering to the research agenda outlined in this report, the NIH can make steady and measurable progress toward closing these gaps and thereby achieve real gains toward bettering the health of all women in the United States. Such progress in the improvement of their health is precisely what the women in this country amply deserve.

## **EXECUTIVE SUMMARY**

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This section provides a brief overview of the report's key findings and recommendations.

The report concludes with a summary of the findings and recommendations.



# EXECUTIVE SUMMARY

## Introduction

At the end of the 1980s, irrefutable national data and statistics pointed to a crisis in women's health: a crisis that has stunned citizens, policy-makers, and the biomedical community. As a Nation, we have long known that three diseases—heart disease, cancer, and stroke—are the major killers of men and women alike. Currently, the number of women who die each year from these diseases are as follows:

- #1 Heart Disease: 365,625 deaths each year
- #2 Cancer: 232,815 deaths each year
- #3 Stroke: 88,220 deaths each year<sup>\*1</sup>

The startling realization is that most of the biomedical knowledge about the causes, expression, and treatment of these diseases derives from studies of men and is applied to women with the supposition that there are no differences. During recent years we looked at the data from a different per-

spective. We asked if there *are differences* in the health of men and women. As the statistics on death and disease specific to women were integrated and interpreted, concerned individuals became acutely aware that health problems specific to women are worsening and that we currently do not have all the knowledge necessary to reverse this trend. The following issues are now glaringly undeniable truths:

- **Women will constitute the larger population and will be the most *susceptible* to disease in the future.**
- **Overall, women have *worse* health than men.**
- **Certain health problems are more *prevalent* in women than in men.**
- **Certain health problems are *unique* to women or affect women *differently* than they do men.**

To focus the biomedical research community on these issues of women's health and to garner their knowledge into a comprehensive plan about

\* In some cases, data presented in this publication are different from those presented in the original working group reports because in the year that has passed since the presentation of these reports, new data have become available. These reports underwent review and revisions with participation and final approval by the cochairs of the respective working groups.

how to systematically and expeditiously address those issues, the Office of Research on Women's Health sponsored the Workshop on Opportunities for Research on Women's Health. The goal of both this workshop and the series of events preceding it was to develop a comprehensive research agenda to investigate women's health issues.

## **Setting a Research Agenda**

As health needs become more widespread in the Nation and funding becomes less available, the goal of solving the health problems facing women must be considered in the design of biomedical research studies. Solving a health problem entails a four-step process (these steps may be simultaneous): recognition, response, research, and reversal.

### **Recognition**

First is **recognition** of the problem. Recognition usually occurs when enough data are available to show a trend, either in rates of disease or of death from disease. The trends may occur among the entire population or within subgroups of the population. The subgroups may be described by such factors as age, sex, ethnicity, race, geographical residence, income, and education level. The data sources typically used for health trends are the U.S. Census (every 10 years), hospital records, insurance company data, epidemiologic studies (studies of patterns of disease and behaviors among populations), and other population studies conducted by the National Center for Health Statistics.

Even with modern methods of data collection and analysis, recognizing and, more so, forecasting health trends are extremely difficult in a society as ethnically and behaviorally complex and as rapidly changing as that of the United States. Identifying the cause-and-effect relationships between disease trends, social change, personal behaviors, cultural composition, and biomedical knowledge is extraordinarily difficult. Assumptions based on logically predicted population patterns may or may not prove to be accurate.

As the nature of our society has changed, so have the behaviors of the population and so have the types of diseases that strike and kill us. At the end of the past century, infectious diseases were the greatest threat; later these were superseded

by heart disease, then cancer, both of which have behavioral and genetic causes; now, with AIDS, infectious disease once again looms as an epidemic. In the future, other disease outbreaks may literally catch us by surprise.

## I S S U E

### **Women Will Constitute the Larger Population and Will Be the Most *Susceptible* to Disease in the Future.**

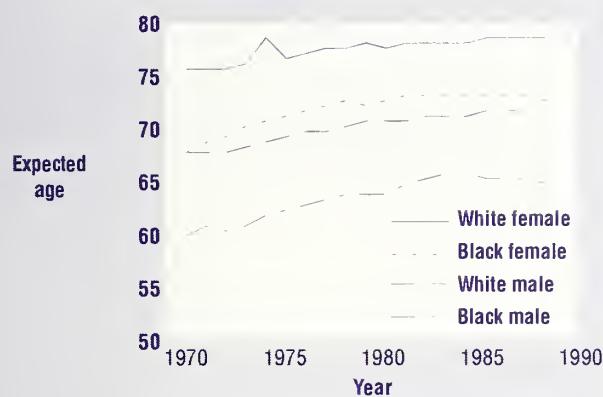
Gathering and analyzing data takes time and is performed in cycles, and therefore we sometimes recognize the emergence of a trend only after it is well underway. Such was the case for the observations about women's health issues. Perhaps another reason for the lag of recognition of the trend in women's health issues is that historically throughout the 20th century, women have had a longer life expectancy than men. For example, for all races in 1900, life expectancy was 46.3 years for men and 48.3 for women; in 1989, 71.8 and 78.6.<sup>2</sup> Figure 1 and Table 1 show the life expectancy for men and women according to race.

**Table 1.<sup>3</sup>**  
***Life Expectancy—1989***

	<b>Men</b>	<b>Women</b>
Total Population	71.8 years	78.6 years
Whites	72.7	79.2
Blacks	64.8	73.5
Hispanics	69.6	77.1
Native Americans	not available	not available
Asian Pacific	not available	not available
Islanders		

At face value, these statistics sound like good news for women; but in fact, interpreted in the context of the future and of certain disease trends, they are ominous. Unfortunately, these figures demonstrate that women, in increasing numbers and more so than men, will be facing the

**Figure 1.**  
***Life Expectancy at Birth According to Race and Sex, United States, 1970-1988***



Source: National Center for Health Statistics. *Health United States, 1990*. DHHS Pub. No. (PHS) 91-1232. Hyattsville, Maryland: Public Health Service, 1991.

**Table 2.<sup>4</sup>**  
***Percentage of Women Within the Aging Population***

	Age 65+	Age 85+
1900	49.5%	55.6%
1980	59.7%	69.6%
1990	59.7%	72.0%
2020	60.0%	73.0%

health problems that accompany old age, for example, osteoporosis and Alzheimer's disease. In 1900, only 4% of the population was age 65 and over and only 0.2% was over age 85; by 1985, percentages had risen sharply to 12% and 1.1%, respectively.<sup>5</sup> In 1900, women constituted 49.5% of the group over age 65, and in 1980, 59.7%. Even more dramatic, they now constitute 72% of the group over age 85.<sup>4</sup> Projections indicate that in the year 2020, there will be 69 men for every 100 women at age 65, and 36 men per 100 women at age 85.<sup>6</sup> Table 2 shows the growth of women as the aging majority in our Nation.

## ISSUE

### Overall, Women Have Worse Health Than Men.

Already, women requiring care in nursing homes or personal care facilities outnumber men three to one (963,900 women and 334,400 men in 1985).<sup>7</sup> In 1990, of the 7 million women over age 75, nearly 2 million were either unable or limited in their ability to carry on major activities.<sup>8</sup>

Throughout their lives, as shown by statistics, the quality of life for women lags behind that for men: women have more acute symptoms, chronic conditions, and short- and long-term disabilities arising from health problems.

- Women's activities are limited by health problems approximately 25% more days each year than are men's activities.<sup>9</sup>
- Women are bedridden 35% more days than men because of infective/parasitic diseases, respiratory diseases, digestive system conditions, injuries, and other acute conditions.<sup>10</sup>

These statistics are true even when reproductive problems are eliminated from the calculations.

## ISSUE

### Certain Health Problems Are More Prevalent in Women Than in Men.

**Cardiovascular Disease.** Nearly 90,000 women die of stroke each year. Stroke accounts for a higher percentage of deaths among women than men in all stages of life.

- Half of all women, but only 31% of men, who have heart attacks die within a year.<sup>11</sup>
- Approximately 90% of all heart disease deaths among women occur after menopause.<sup>11</sup>
- One in 9 women ages 45-64 has some clinical cardiovascular disease, rising to 1 in 3 at age 65 and older.<sup>11</sup>

**Mental Disorders.** The rate of affective disorders is almost twice that for women, about 7%, compared with men.<sup>12</sup> In elderly women, the prevalence of depression is 3.64% versus 1% in men.<sup>13</sup>

**Alzheimer's Disease.** Occurrence of this disease is higher among women than men, and it increases with age—dramatically so after age 85.

#### Osteoporosis.

- Osteoporosis affects over 24 million Americans, primarily women.<sup>14</sup>
- Osteoporosis affects one-third to one-half of all postmenopausal women.<sup>14</sup>
- The rates for osteoporosis increase dramatically for women with age, as shown in Table 3.

**Table 3.<sup>15</sup>**  
**Rates of Osteoporosis in Women**

Age Group	Rate
45-49	17.9%
50-54	39.2%
55-59	57.7%
60-64	65.6%
65-69	73.5%
75+	89.0%

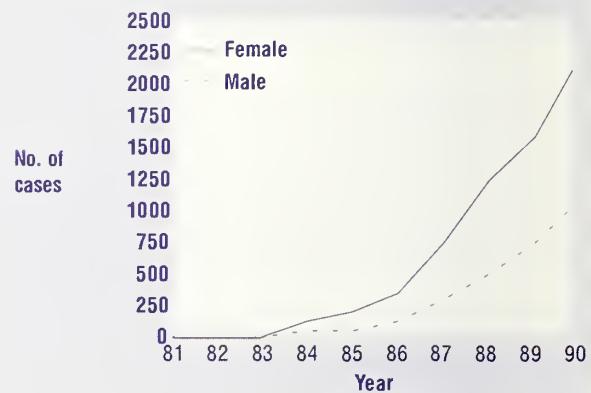
- Hip fractures are the most serious consequence of osteoporosis. Each year, 250,000 people are hospitalized with hip fractures and are temporarily disabled. About one-third will become totally dependent, and one-half will never walk independently again.<sup>14</sup>
- Osteoporosis causes 1.3 million bone fractures every year.<sup>14</sup>
- Annually, 500,000 vertebrae fractures occur. Nearly one-third of women over age 65 will suffer at least one vertebral fracture.<sup>14</sup>

#### Sexually Transmitted Diseases.

- Each year, 6 million women in the United States, half of whom are teenagers, acquire a sexually transmitted disease.<sup>16</sup>
- Fifteen to 20 million women are chronically infected with either genital herpes or human papillomavirus (HPV) infections.<sup>16</sup>

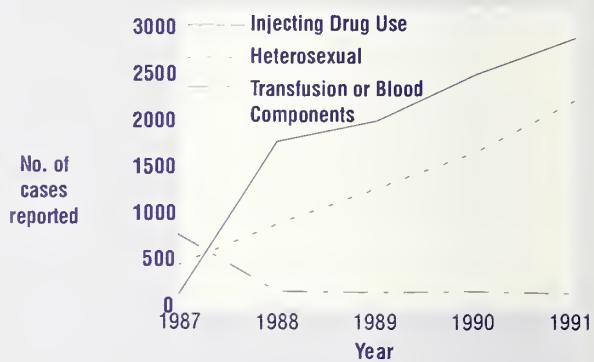
- Women are the fastest growing population with AIDS; IV drug abuse and heterosexual contact are the primary modes of transmission (Figures 2 and 3).

**Figure 2.**  
**AIDS Cases Through Heterosexual Contact With Persons With, or at High Risk for, HIV Infection**



\*Figures are based on cases reported through March 1991 and adjusted for reporting delays.  
Source: MMWR 40 (22): 357-9, 1991.

**Figure 3.**  
**AIDS in Women by Exposure Category Cases Reported 1987 Through 1991**



Source: Office of AIDS Research, National Institutes of Health.

### **Immunologic Diseases.**

- Autoimmune thyroid diseases have a 15:1 ratio of women to men.<sup>17</sup>
- Rheumatoid arthritis has a 3:1 ratio of women to men. Rheumatoid arthritis leads to disability and decreased life expectancy.<sup>17</sup>
- Systemic lupus erythematosus (SLE) occurs nine times more often in women than men. There are 500,000 cases of SLE in the United States.<sup>17</sup>
- Systemic sclerosis affects women four times as often as men.<sup>17</sup>
- Diabetes mellitus and multiple sclerosis occur more often in women.<sup>17</sup>

### **Disability.**

- More women than men of every age group report or seek care for illness and disability.
- More women than men seek care for acute conditions and short-term disabilities that occur during the reproductive years (ages 18-44). For example, in 1985, for every 100 persons, women had 49.7 bouts of influenza, men 37.0; women had 30.7 common colds, men 21.4. Some of the excess of acute illness may be explained by women's greater exposure to school children with childhood infections.<sup>18</sup>
- More women than men seek care for chronic conditions and associated disability in mid- and late life. For example, for every one man, 6.5 women seek care for thyroid diseases, 4.8 women seek care for anemias, 4 women seek care for spastic colon, 3.5 for frequent constipation, 1.6 for gallstones, 1.6 for arthritis, and 2.0 for chronic bronchitis.<sup>18</sup>

## ISSUE

### **Certain Health Problems Are *Unique* to Women or Affect Women *Differently* Than They Do Men.**

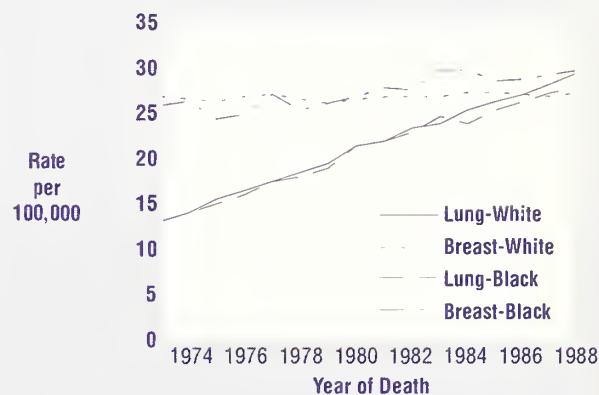
#### **Cancer.**

- While cancer is the second leading cause of death among American women of all ages, accounting for 250,000 deaths each year, it is the leading cause of *premature* death.<sup>19</sup>

- Lung cancer has surpassed breast cancer as the leading cause of cancer death in women (Figure 4). In 1991, 51,000 women died from lung cancer, and 45,000 women died from breast cancer. This rate parallels the rate of increase in smoking among women. Lung cancer is almost entirely due to cigarette smoking. Today, more young women become smokers than young men.<sup>19</sup>

**Figure 4.**

### **Breast vs. Lung Cancer Mortality White Females vs. Black Females United States, 1973-88**



Age-Adjusted to 1970 Standard.

- Approximately 27% of cancer deaths among women are accounted for by cancers of the breast (44,000) and of the reproductive system—ovarian (12,500), cervical (4,500), uterine (5,500).<sup>19</sup>
- The death rate from breast cancer between 1979 and 1986 increased an overwhelming 24%. Today, 1 in 9 women will develop breast cancer<sup>20</sup> whereas in the 1960s, the rate was only 1 in 20.<sup>20</sup>

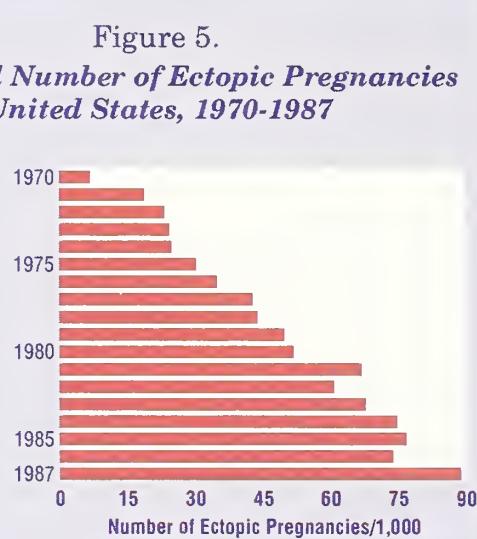
#### **Sexually Transmitted Diseases (STDs).**

- Two and one-half million women acquire chlamydial genital infections annually.<sup>21</sup>

- One million women are treated for pelvic inflammatory disease annually.<sup>21</sup>
- During the past decade, because of STDs, the cases of involuntary infertility and ectopic pregnancies have quadrupled (Figure 5).
- Over 19,000 cases of AIDS in women have been reported to the Centers for Disease Control (CDC) and an estimated 200,000 women may be infected with HIV.<sup>21</sup>
- As a result of perinatal transmission, AIDS is the leading cause of death among Hispanic children and the second leading cause of death for Black children.<sup>21</sup>

#### Pregnancy-Related Problems.

- The rate of ectopic pregnancies (those occurring in abnormal positions or places) quadrupled between 1970 and 1987 (Figure 5).
- Fetal and perinatal deaths are 3 to 8 times greater in pregnancies of diabetic mothers than nondiabetic mothers.<sup>22</sup>
- Congenital malformations in children of diabetic mothers are several-fold more common than in those of nondiabetic mothers.<sup>22</sup>



Source: National Hospital Discharge Survey, National Center for Health Statistics.

- Of women who have gestational diabetes,<sup>22</sup> about 25% will develop diabetes mellitus.<sup>22</sup>
- Over 100,000 infants die or suffer birth defects because of STDs transmitted during pregnancy or at birth.<sup>21</sup>

## From Recognition to Response

Once the statistics on women's health issues through the 1980s were available, consolidated, and interpreted, the NIH realized that insufficient scientific knowledge exists about the unique problems of women's health, knowledge necessary to control and reverse the causes and effects of those problems. The NIH's establishment of the Office of Research on Women's Health has accelerated the response and has not lagged in responding to the issues and to that deficit. The response to develop a comprehensive research agenda which would provide the knowledge base for the trends has been as immediate as feasible. Within only 1 year of its establishment, the ORWH had planned and implemented a public hearing and the Workshop on Opportunities for Research on Women's Health.

If we are to have answers, we must ask questions, and those questions must be the right questions. Recently, we have come to realize that health research has not asked enough of the right questions about women, or else has not asked them in the appropriate way, including looking at women themselves as research subjects. Therefore, we do not have the answers for a multitude of health care and disease prevention issues relevant to women.

A comprehensive research agenda on women's health must have a multidisciplinary approach to all age segments of a woman's life span. The studies proposed in such an agenda must investigate not only the biologic factors of health issues, but also the lifestyle (behavioral), racial, ethnic, age, sex, and socioeconomic reactors that influence health status. The agenda, therefore, must include basic, clinical, behavioral, and epidemiologic research studies. Above all, women must be included as subjects in the research studies.

#### Socioeconomic Factors

The two major predictors of poor health are poverty and lack of education. In a series of self-reports, 52% of high-income individuals but only 28% of low-income individuals rated their health as excellent.<sup>23</sup> Poverty and lack of education in the United

States tend to be disproportionately higher among certain ethnic and racial groups, especially Blacks and Hispanics. Table 4 compares the poverty rates of four ethnic groups with their percentage of representation in the total U.S. population. Blacks, Hispanics, and Native Americans have especially high rates of poverty.

**Table 4.<sup>24</sup>**  
**1990 Population Data—United States**

	% of Total U.S. Population	Poverty Rate %
Blacks	21.1	31.9
Hispanics (Mexican Americans, Puerto Ricans, Cuban Americans, South/Central American, Caribbean)	9.0	28.1
Native Americans	0.8	28.2
Asian/Pacific Islanders (Chinese, Japanese, Korean, Filipino, Indian, South East Asian)	2.9	12.2
Total U.S.	100	13.5

Poor people have less access to health care and less health insurance. For example, 32% of Hispanics and 20% of Blacks are uninsured whereas 13% of whites are insured.<sup>25</sup> Poverty groups are especially hard hit by rising health care costs.

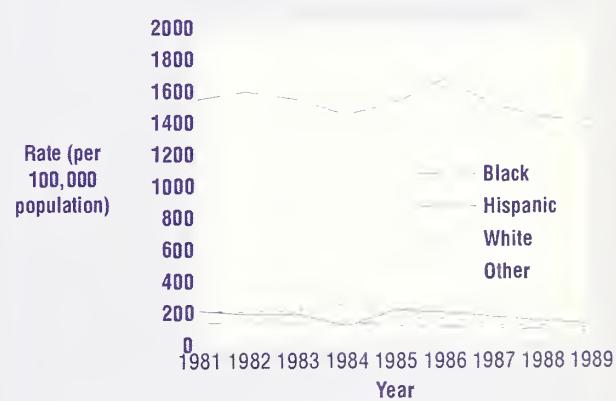
### Ethnic and Racial Diversity

Health status varies among the different subgroups of the American population. Epidemiologic data, analyzed by ethnic and racial subgroups, are lacking for many health conditions, but the following facts indicate that variation does exist and that research must be responsive to those factors.

- Death from stroke occurs twice as often in Black women as in white women.<sup>26</sup>
- Rates of death from coronary heart disease are higher for Black women than for white women, 172.9 versus 106.6 per 100,000 persons.<sup>27</sup>

- The rate of death from complications of pregnancy and childbirth are 3.5 times greater for Black women than for white women. Ectopic pregnancies are the main cause of pregnancy-related deaths among Black women.<sup>28</sup>
- Systemic lupus erythematosus occurs 3 times more often in Black women than in white women.<sup>29</sup>
- The occurrence of adolescent pregnancies is highest among Blacks—23%—and lowest among Asian Americans—6%.<sup>30</sup> The birth rate among Black girls under age 15 is 7 times higher than for white girls.<sup>31</sup>
- The incidence of breast cancer is *lower* for Black women than for white women, but death rates from breast cancer are *higher* for Black women than for white women (Figure 4).
- Rates for lung cancer are higher for white women than for Black women (Figure 4).
- Among Hispanics, death rates from homicide, AIDS, and perinatal conditions are greater than for whites.<sup>32</sup>
- Black women have the highest incidence of gonorrhea and syphilis (Figure 6).

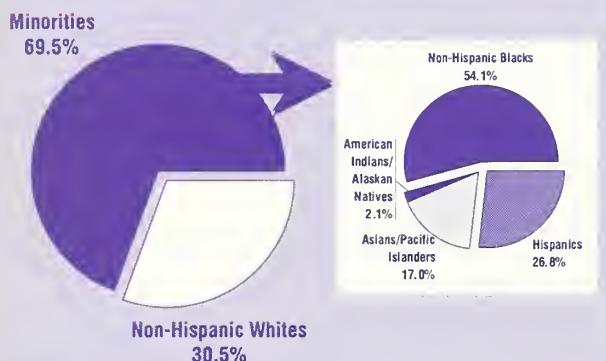
Figure 6.  
**Trends in the Incidence of Syphilis in Women in the United States According to Race and Ethnicity, 1981-1989**



Adapted from Rolfs RT, Nakashima AK. JAMA 264:1432-7, 1990.

- Although overall incidence of cancer is lower for Hispanic women, certain specific cancer rates are higher:
  - The incidence of cervical cancer among Hispanic women is double that for non-Hispanic white women.<sup>25</sup>
  - Death due to stomach cancer is twice as high for Hispanics as for non-Hispanic whites.<sup>25</sup>

**Figure 7.**  
**Total Tuberculosis Cases,**  
**United States, 1990**



Source: MMWR 41 (RR5): 2, 1992.

- The incidence of tuberculosis among Blacks and Hispanics is four times that of non-Hispanic whites (Figure 7).
- The prevalence of noninsulin-dependent diabetes mellitus is twice as high among Black women as among white women.<sup>33</sup>
- Hispanics have 3 times the risk of developing diabetes and greater metabolic severity than non-Hispanic whites.<sup>34</sup>
- Prevalence of noninsulin-dependent diabetes mellitus is 2 to 5 times higher among Native Americans than among other U.S. populations;

68% of Pima Indian women 55 to 64 years of age have noninsulin-dependent diabetes mellitus.<sup>33</sup>

- Hispanics are disproportionately affected by AIDS. Hispanic women constitute 15.8% of all women with AIDS, and Hispanic children, 20.5% of all children under age 13.<sup>35</sup>
- Obesity is a major risk factor for cardiovascular disease, stroke, and other diseases; 44% of Black women, 42% of Mexican-American women, 40% of Puerto Rican women, 31% of Cuban women, and 24% of white women are overweight.<sup>36</sup>

#### **Behavioral Factors**

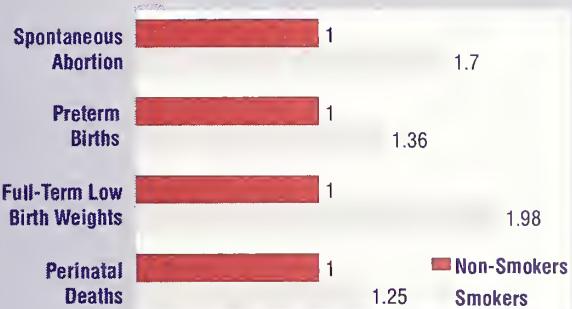
- Behavioral factors undeniably contribute to the development of disease. The single most detrimental behavior is cigarette smoking, and women are more likely than men to start smoking and less likely to quit. One of the tragedies of the mid-20th century has been the uptake of cigarette smoking by women. Men began smoking cigarettes in large numbers immediately before and during World War I, and their death rates from lung cancer began to rise 20 years later. Women began smoking intensively during World War II, and 20 years later their lung cancer death rates began to rise, too. Now, lung cancer surpasses breast cancer as the chief cause of cancer death among women.

The rate of smoking by women increased from 18% to 34%, 1935 to 1965. Adolescent girls are beginning to smoke at a rate of 29%.<sup>37</sup> Other health consequences associated with smoking are:

- Lung and other cancers
- Heart disease
- Hypertension
- Osteoporosis
- Respiratory diseases
- Spontaneous abortions, preterm births, and low-birth-weight infants (Figure 8)
- Fetal and infant deaths.

These diseases are increasing among women who smoke.

**Figure 8.**  
**Risks From Smoking During Pregnancy**



Source: US Department of Health and Human Services, Office on Smoking and Health. The health consequences of smoking for women. A report of the Surgeon General. Rockville, Maryland: Public Health Service, 1980.

Early prenatal care is important for early diagnosis of abnormalities and for timely and appropriate intervention.

### **Women as Subjects in Research Studies**

Women are underrepresented in the subject populations of biomedical research, especially pregnant women and women of childbearing age. For example, in 1981, studies on the prevention value of aspirin for coronary artery disease were begun. These studies were conducted almost exclusively on men, but recommendations were put forth for the general population without any knowledge of how women react to drug therapies—in the absorption of the drugs, the benefits achieved, and the pathways by which drugs are eliminated from the body. An example of an implication is that if a drug is eliminated from a woman's body more slowly than from a man's, the woman might have a greater risk of side effects or might need a lower dosage. Furthermore, hormonal changes during the menstrual cycle may alter the effects of drugs in women, as noted in the use of antidepressant drugs. Why have women often been

Other important behavioral factors and facts are:

- **Diet:** High fat consumption may contribute significantly to the development of heart disease and of cancers in postmenopausal women.
- **Sexual Activity:** American girls are sexually active at younger ages, leading to increases in teenage pregnancy and sexually transmitted diseases, including AIDS. Among girls 15 years old, 25% are sexually active.<sup>38</sup>
- **Use of Contraceptives:** Eighty percent of sexually active women have used oral contraceptives at one time or another. The long-term effects are not known, but there is concern that oral contraceptives contribute to the risk of breast cancer.<sup>39</sup>
- Women who use oral contraceptives substantially increase their risk of heart disease if they smoke.<sup>40</sup>
- **Prenatal Care:** Use of prenatal care varies among population subgroups (Figure 9).

**Figure 9.**  
**Proportion of Mothers With Early Prenatal Care, According to Race and Ethnicity of Mother: United States, 1989**



Note: Early prenatal care is defined as care beginning in the first trimester of pregnancy. Late prenatal care is defined as care beginning in the third trimester. Data on Hispanic origin of mother are from 30 States and the District of Columbia.

Source: National Center for Health Statistics, National Vital Statistics System.

excluded from research? Some of the stated reasons have been:

- Women's cyclical hormonal changes confound research results.
- Study populations would be less homogeneous.
- Study costs would be higher if gender-specific hypotheses or subgroup analysis are anticipated.
- Recruitment of women into studies is more difficult.
- Wariness since the thalidomide tragedy and anticipation of legal and ethical issues surrounding potentially harming a fetus in a pregnant or potentially pregnant woman.
- Pervasive sense in the research community that many of the health issues of women are of secondary importance, especially those that occur solely in women and those that occur in men and women but have already been studied chiefly in men.

To address the issues of including women in clinical research, the ORWH requested that the Institute of Medicine prepare a report analyzing the perceived obstacles to the inclusion of women as research subjects and recommending feasible means of overcoming them. The preliminary analyses suggest a number of general approaches for dealing with the financial, legal, and ethical issues involved in recruiting and including women in clinical research.

### **Women in Biomedical Careers**

The development and successful implementation of a research agenda on women's health derives in part from the leadership of women in influential positions as policymakers, principal investigators, and teachers. Therefore, ORWH has undertaken a series of projects to identify the problems in attracting women to and retaining them in these positions and to develop a plan for overcoming the barriers to biomedical careers for women.

The statistics and issues relevant to the paucity of women in biomedical research careers are detailed in the Summary of the Hearing on Women in Biomedical Research Careers (see Appendix 7).

### **From Response to Research and Reversal**

In order for advances in scientific knowledge and biomedical technologies to be achieved through this research agenda, the proposed recommendations for research must move promptly through the **research** cycle: approval, funding, implementation of the studies, analysis, and interpretation of the practical significance of the research results. These results can then be applied to patient care with full knowledge of the racial, ethnic, and age differences in effectiveness.

Scientists, practitioners, patients, and the public, of both genders, must be sensitized about the need, value, and benefits of such directed research and treatment. The research agenda for women's health issues is a vehicle for addressing past gender inequalities and, hopefully, for guiding undertakings by other Federal agencies, academic institutions, pharmaceutical manufacturers, and public and private sector agencies and organizations. Through this agenda, the trend can be **reversed**; the goals of improving women's health and the quality of life of our Nation's women of all ages and races will become an integral part of biomedical and biobehavioral initiatives.

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## The Research Agenda for Women's Health

The 10 subsections that follow are synopses of the 10 working group reports. The full reports constitute Part Two of this document and are highly scientific in nature and language, especially the recommendations for research studies. To render those reports comprehensible to the lay person, the synopses in this executive summary have been prepared in less technical language. Each synopsis summarizes the major themes of the working group topic in text form and, in list form, presents highlights of the biologic, biomedical, and epidemiologic areas which the recommended research studies would investigate. The lists are not all-inclusive of every recommendation, but are representative of the areas. Those seeking indepth detail and all of the recommendations are encouraged to read Part Two of this document.

## The Ten Working Groups

### Life Span

Birth to Young Adulthood  
Young Adulthood to Perimenopausal Years  
Perimenopausal to Mature Years  
Mature Years

### Crosscutting Science

Reproductive Biology  
Early Developmental Biology  
Aging Processes  
Cardiovascular Function and Disease  
Malignancy  
Immune Function and Infectious Diseases

## **Birth to Young Adulthood**

**(*birth to 15 years of age*)**

### **Themes**

In no other portion of a woman's life span do such dramatic changes occur as during the nearly 2 decades between birth and young adulthood.

Beyond the first year of life, the prevalence, incidence, and costs of death and ill health among girls and young women are related less to disability and disease than to injuries, environmental exposures/ hazards, and risk taking. Injuries, including acts of physical and sexual violence, are the leading cause of death and ill health among girls and young women.

Many of the diseases that cause significant ill health and death among adult women have their onset in childhood and adolescence. Choices about

lifestyle made during these years can have a profound impact on later susceptibility or resistance to disease; however, the range of choices may be limited by economic or cultural conditions. By the time girls enter adolescence, gender differences in mental health are clearly established, as measured by rates of depression and suicide gestures.

About 10 percent of children and youths have a chronic disease or physical disability. Some of these conditions (autoimmune disorders such as lupus erythematosus and juvenile rheumatoid arthritis, scoliosis, and thyroid disorders) are more prevalent among girls and/or have their onset or worsen during puberty.

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### **The Working Group on Birth to Young Adulthood recommended that researchers study:**

- Whether or not male and female fetuses develop differently during pregnancy.
- The effects of a mother's health and health practices on the health of the fetus, the newborn, and herself. Examples of health practices include treatment the mother is undergoing for preexisting disease; depression and stress; ethnic characteristics; breastfeeding; and alcohol, drug, and tobacco use.
- What constitutes normal development during the first 15 years of life.
- The causes of greater incidence of obesity in certain ethnic groups.
- Whether factors such as alcohol, drug, and tobacco use; the environment; and social pressure cause more injuries leading to death or disability among girls than boys.
- The reaction of girls to the divorce of their parents, compared with boys.
- The connection between family violence—such as physical or sexual abuse—during this age and risk-taking behaviors such as early unprotected sexual intercourse; delinquency; and tobacco, drug, and alcohol use.
- The factors contributing to girls' self-esteem.
- Ways to eliminate eating disorders and other psychological problems.

# **Young Adulthood to Perimenopausal Years**

## **(15 to 44 years of age)**

### **Themes**

Overall, the rate of death in the United States among women 15 to 45 years of age is relatively low (79 per 100,000 in 1988). In that same year, the leading causes of death in this age group included injuries (unintentional, suicides, and homicides), heart disease, cancer, AIDS, and liver disease. Deaths from cardiovascular diseases, homicides, and AIDS are much higher among Blacks than among whites.

The years from young adulthood to menopause should be a woman's most productive years, not only as a member of her society and her family,

but also in terms of personal growth. Yet, because these are also the reproductive years, optimal productivity and personal development depend in large measure upon a woman's ability to live free of disease in terms of sexual function, fertility regulation, pregnancy, and delivery. Critically important health issues are therefore prevention and control of sexually transmitted diseases, including AIDS. A number of conditions in women prior to menopause may cause disability or death: depression, substance abuse, sexual and physical abuse, injuries, cancers, and cardiovascular diseases.

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### **The Working Group on Young Adulthood to Perimenopausal Years recommended that researchers study:**

- What can be done to prevent women from getting sexually transmitted diseases, including AIDS.
- How the transmission of AIDS from the mother to the fetus can be prevented.
- The development of safe forms of contraception, such as reversible sterilization and new oral contraceptives.
- How fertility can be enhanced.
- How pregnancies at risk of miscarriage can be maintained.
- What can be done to ensure that each pregnancy results in the delivery of a normal, healthy baby.
- What can be done to prevent hysterectomy, infertility, and early fetal loss if a woman suffers from endometriosis or fibroid tumors.
- Treatments for women who suffer from chronic pelvic pain.
- The characteristics of premenstrual syndrome.
- Why so many more women than men suffer from depression after puberty.
- The causes of the increase in illicit drug and alcohol use among women.
- How widespread physical and sexual abuse are among women, and what the physical and psychological effects are immediately and later on in life.
- Why injury is the overall leading cause of death among women ages 15 to 44, and what can be done to reduce injuries of all types, including motor vehicle accidents, drownings, poisoning, fires and burns, gunshot wounds, and suicides.
- Methods to be implemented during this life segment for preventing lung, breast, colorectal, uterine, and ovarian cancers in later years.
- Methods to be implemented during this life segment for preventing heart disease and stroke in later years.

## **Perimenopausal to Mature Years**

**(45 to 64 years of age)**

### **Themes**

The perimenopausal to mature years are unique in a woman's life, in part because of the occurrence of menopause. Also during these years, many of the major chronic conditions may first appear. These include heart disease, cancer (especially of the breast and colon), arthritis, osteoporosis, depression, diabetes, disability, and injury. The prevalence of many of these conditions is high, and the rates of some increase markedly from the beginning to the end of this age span. One out of seven women in this age range already has clinical heart disease; lung cancer is the leading cancer killer; and breast cancer is the second. One-third of U.S. women have had a hysterectomy by age 54, a much higher prevalence than in most other industrialized societies. And approximately 3 percent of women in this age group will experience a major depressive episode.

The prevalence of these health problems varies in minority women. For example, diabetes, a major

cause of ill health, is two to three times more common in Blacks, Hispanics, and Native Americans than in whites.

While menopause is the major physiologic event during this part of the life span, the perimenopausal to mature years also encompass major transitions in social roles and life circumstances for women. For example, a substantial number of women will be widowed or divorced during this period, increasing the possibility of social isolation. Such changes may affect physical and emotional health.

The physical and psychological changes that occur during this part of a woman's life span are complex, and her health is measured by more than just the absence of disease. Research on the middle years of a woman's life must be a high priority and must take into account a woman's health in the broadest sense of the word.

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### **The Working Group on Perimenopausal to Mature Years recommended that researchers study:**

- The effects of hormone replacement therapy on heart disease; breast, uterine, and other cancers; osteoporosis; and mental health.
- The changes that occur in a woman when she reaches menopause.
- The effect of early menopause on the health of women.
- The psychological, physical, and emotional effects on women as they change roles.

## Mature Years

### (65 years of age and older)

#### Themes

Women constitute approximately 59% of the U.S. population age 65 and older. Among people age 85 and older—a group expected to double in the coming decades—women make up nearly three-fourths of the population. Women as a group share a biological and psychological sturdiness that has afforded them a distinct survival advantage such that, throughout the industrialized world, they survive 4 to 10 years longer than men. Women survive through the decades that claim their male counterparts with cardiovascular disease and cancer, providing care and succor; however, when women develop these diseases, they may no longer have available social supports or caregivers for themselves. In addition, if women survive the common diseases of earlier life, many will live long enough to develop the devastating illnesses that are unique to the very old.

One goal of research is to make the duration of time spent in a frail state as brief as possible before death. These issues are important because

it is the frailty and accumulated illnesses of the elderly that not only strain the health care system, but also deprive the old of dignity and a good quality of life in their last years. In addition, women in their mature years experience significant psychological and social changes. These include losses of many types (e.g., death of loved ones, end of employment, decreased income), maladaptive illness and health behaviors, and transitions between roles (from wife to widow, or having to function as parents for one's own parents). Since women are often the major caregivers, they experience these changes most acutely. Potential consequences include increased vulnerability and loss of control over one's body, a decline in self-care, and loss of work-related self-esteem, possibly accelerating or accelerated by the onset of frailty and dependency. The impact that these changes have on survival is most pronounced for women of lower socioeconomic status. This fact gives rise to many culturally and ethnically relevant questions.

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#### The Working Group on Mature Years recommended that researchers study:

- The long-term physical and mental effects of menopause for women over 65 years of age.
- Whether the use of alcohol, tobacco, prescription and nonprescription medications, and illicit drugs has any affect on the development of physical and mental disability in women over age 65.
- Whether mature women in different social and ethnic groups suffer different disabilities.
- What can facilitate women in this age group seeking and obtaining preventive health care services.
- Ways that health care workers can be made aware of the special problems faced by women over age 65.
- What measures can lead to an improvement in women's self-esteem during this part of the life span.
- How economic, social, or ethnic health habits are reflected in the health of the mature woman.
- Specific barriers to access and utilization of health care.
- The psychological as well as biological implications of caregiving for and by the mature woman.
- The ways potential institutionalization and fear of dependency can impinge on women's health.
- If the increased prevalence of depression among mature women can be prevented or reversed.
- Ways that the ethical issues of providing or withholding care can be confronted in light of the recognition that the latter decision is essentially equivalent to rationing of care.

# Reproductive Biology

## Themes

Reproduction is one of the least understood of all bodily functions due to the complexity of the systems that govern all aspects of the reproductive process. A major portion of female reproductive disturbances, such as infertility and menstrual dysfunction, are related to ovarian dysfunction, which can affect not only the reproductive capacity of the individual, but may also jeopardize general health. Provocative evidence indicates that ovarian hormones, cognitive function, and emotional behavior are interrelated. During times of rapid hormonal change—such as puberty, the years surrounding menopause, the years that follow it, and the period after giving birth—the behaviors of women change. The postpartum state has

been associated with documented depression and severe psychopathology. The burden of preterm birth cases falls heavily on lower socioeconomic groups and women of color. Most of these and other disturbances in the reproductive health of women can only be prevented and treated if the basic physiology of the reproductive system is understood. Research into the mysteries of reproduction can expand our understanding of fertility and infertility and help in designing more effective methods for restoration of fertility and contraception. Some of the areas that, with intensive exploration, can greatly influence reproductive health include the functions of the brain; pituitary, uterus, and mammary glands; and ovaries.

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## The Working Group on Reproductive Biology recommended that researchers study:

- How the hormones that control the workings of a woman’s ovaries and other organs of the reproductive system are released and regulated within her body.
- How a woman’s environment (e.g., diet, exercise, light/dark cycles) or mental health can affect this process.
- How the glands that control a woman’s ovulatory cycle change from girlhood to puberty, during her reproductive years, and during and after menopause.
- Whether these glands operate differently across these life cycles among different ethnic groups.
- Whether sex steroids can be used safely to regulate the glands that control a woman’s ovulation cycle.
- Whether contraceptive methods can be improved by manipulating the glands that control a woman’s ovulation cycle and possible alternative methods.
- Ways to improve infertility treatments.
- Methods for controlling hot flashes.
- What is necessary for normal development of the follicles—from among the 2 million follicles present within the ovaries of a female infant at birth—that are released during ovulation across a woman’s life span.
- How the body reacts when the supply of follicles is exhausted well before the expected time of menopause, and ways this premature menopause can be prevented.
- Whether fertility can be restored by stimulating follicle growth or secretion of progesterone, and whether new contraceptive techniques can be identified by the same means.
- Whether frequent pregnancy losses can be prevented by increasing progesterone hormone levels in the early weeks of gestation.

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- Treatments for women who have an excess of male hormone.
  - Ways for controlling the abnormal uterine bleeding, infertility, and increased risk for endometrial cancer that often accompany polycystic ovary syndrome (PCOS).
  - Whether PCOS occurs within different ethnic groups with the same frequency and why.
  - Whether PCOS is a genetically inherited disease that is passed on through families.
  - Ways of reversing or modifying the effects of ovarian hormone deficiencies—bone loss, vaginal dryness, increased risk of cardiovascular disease, hot flashes, depression.
  - The extent to which stress, substance abuse, race, and maternal age contribute to preterm labor and premature delivery of an infant.
  - The extent to which a woman can prevent premature delivery of her baby through diet, vitamins, and psychological support.
  - What constitutes normal uterine behavior during pregnancy, and what induces labor at full term when the fetus is mature.
  - During puberty, how the brain changes, and how this change is linked to moodiness, depression, impulsiveness, or other negative emotions.
  - Whether there is a biological basis for the risk-taking behaviors that so often are undertaken by adolescent girls.
  - Whether puberty occurs earlier among different ethnic groups.
  - Whether gender differences are learned or hormonal; for example, whether reproductive hormones influence mathematical and verbal ability.
  - How hormones contribute to postpartum depression.
  - How hormone replacement during menopause affects a woman's behavior.
  - Whether certain personality types are at high risk for premenstrual syndrome or whether personal or social risk factors contribute, such as stress, nutrition, exercise, and aging.
  - If breast growth and development can or should be regulated.
  - How hormones stimulate or suppress a woman's supply of breast milk.
  - It has been reported that 25% of women in their 30s and 40s have endometriosis, yet retrograde menstrual flow occurs in at least 90% of cycling women. Research is needed to determine if retrograde menstrual flow is responsible for endometriosis. If so, why are some women's bodies able to reject this aberrant tissue? Why don't all women develop this disease? And does a women's immune system determine whether endometrial cells implant?
  - Why endometriosis sometimes occurs at extrapelvic sites, leading to endometriosis of the lung, brain, nose, or bone, (to name just a few).
  - The long-term consequences of endometriosis.
  - How the risk of bone loss that occurs in women with endometriosis can be overcome and how normal bone replenishment can be preserved to prevent osteoporosis.
  - Symptoms for endometriosis are not always accurate indicators of the disease—mild disease may cause debilitating pain whereas severe disease with extensive scarring may be painless; diagnostic techniques should be improved.
  - How therapeutic and surgical treatments for endometriosis can be minimized and improved.
  - Benign fibrous tumors of the uterus are different from ovarian tumors and occur in approximately 40 percent of women—why they occur must be determined.
  - Whether fibroids are manifested differently among women of various races.
  - The relationship between fibroids and pelvic pain, uterine bleeding, and infertility.
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# Early Developmental Biology

## Themes

The outcome of pregnancy can affect a multitude of health issues over a woman's lifetime. Complications such as preterm birth can greatly compromise a child's growth and development, and the consequences of caring for a handicapped infant and child can have devastating effects on health and the quality of life for a mother and for her entire family. By the year 2000 the number of working women in the American workforce will be at its height, and the health of these women during pregnancy and childbearing is of paramount importance to the Nation.

Momentous advances in our understanding of human development and growth are occurring,

primarily because of technological innovations in molecular biology and genetics and the establishment of new methods for studying the development process. As these advances are applied to the developing human fetus, obstetricians, gynecologists, and pediatricians must draw from this new knowledge and apply its practical benefits to the lives of women and their children. The scope of this application of early developmental biology is surprising in its relevance and promise for improving quality of life; it touches not only birth defects and pregnancy, but also repair of the nervous system in aging women and new treatments for cancer.

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## The Working Group on Early Developmental Biology recommended that researchers study:

- How to prevent preterm birth and birth defects.
- Whether identifying and cloning genes can lead to preventing inherited defects, such as cystic fibrosis and muscular dystrophy.
- Whether it is possible to discover new therapies for preventing and treating cancer and inherited defects through molecular genetics.
- Whether mothers and fetuses from different racial groups respond differently to environmental factors and to drug therapies in genetically determined ways.
- How information about the way cells work makes a difference in the lives of doctors and patients.
- What occurs when the gene from the mother versus from the father is inactive, and how this contributes to successful childbearing now and in the next generation.
- How successful and normal implanting of the embryo can be fostered.
- How knowledge about the way tissues organize into organs and acquire specific functions can help prevent birth defects such as congenital dislocated hip and anencephaly, which predominate in females.
- How the transfer of vital nutrients (e.g., glucose, amino acids, fatty acids) and growth-promoting hormones through the placenta can be encouraged so that newborns have healthy birth weights.
- Why birth weights vary among different ethnic groups.
- How habitual abortion and toxemia can be prevented and treated.
- What a mother can do to help her fetus develop a healthy nervous system rather than be born with compromised motor or cognitive abilities or emotional dysfunction.

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- What can be done to repair both the injured and aging nervous system in women.
  - How information about the effects of drugs on the developing fetus can be improved so that pregnant women are neither deprived of needed treatment nor is the fetus exposed to harmful substances.
  - Development of more precise and accessible, less expensive, and risk-free methods for screening pregnant women by noninvasive technology and for monitoring the fetus.
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# Aging Processes

## Themes

Growing older, it is now recognized, does not necessarily entail a universal and inevitable decline in physiological and psychological function. Instead, different organs, different systems, and different individuals age at different rates. This great diversity has clinical implications: it suggests that, in many cases, there may be opportunities to devise interventions to enhance the health, functioning, and sense of well-being of individual older women.

The reasons for this variability in patterns of aging are not understood. It is not known why some women (and men) are able to retain relatively good functional capacity into their later years, whereas others experience a progressive or even sudden decline in function. Major functional impairment is present in approximately 5% of persons ages 65-74, and 35% of those 85 and older. Many of these alterations are the result of a complex interaction among diseases (both current conditions and the consequences of diseases that occurred

in earlier years), lifestyle, nutrition, psychological status, and social support. Beyond age 80, a variety of noncardiovascular disorders, including arthritis, dementia, and neurosensory disorders, account for an increasing burden of disability.

Better epidemiologic data on the antecedents, risk factors, protective factors, and natural history of age-related disability are needed for planning long-range policies that pertain to the elderly. A major research topic is postmenopausal hormone replacement therapy. When levels of ovarian hormones are deficient, postmenopausal women may be at risk for accelerated bone loss and therefore subject to greater risk of fracture, coronary heart disease (due in part to changes in cholesterol and other factors), and symptoms such as hot flashes and urinary incontinence. Other topics of high priority are osteoporosis, dementia (including Alzheimer's disease), cancer, heart disease, nutrition, and disability.

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## The Working Group on Aging Processes recommended that researchers study:

- How women differ from men in the way they age.
- The factors that contribute to healthy aging.
- The genetic factors that contribute to a long life.
- Whether such vitamins as A, C, and E, and food supplements such as calcium can prolong life, promote health, and counter the effects of aging.
- The early signs of diseases, such as atherosclerosis, in women and how they differ from early signs in men.
- Whether women are at greater risk for Alzheimer's disease than men, especially at most advanced ages.
- The genetic factors that protect against such diseases as Alzheimer's and Parkinson's.
- How aging affects the immune system and the impact this has on diseases common in older women (such as lupus and rheumatoid arthritis) and on an older woman's risk of developing cancer.
- How exercise can promote healthy aging in women.
- Whether pregnancy contributes to the development of musculoskeletal problems later in life.
- The impact of prior illness or multiple illnesses on the physical and mental health of older women.
- The role of racial, ethnic, socioeconomic, and health-related behaviors in the development of chronic disorders in older women such as osteoporosis and diabetes.

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- Whether estrogen replacement therapy can help prevent Alzheimer's disease.
  - How mental processes are affected by aging.
  - How changes in mental function and memory affect health behavior in older women.
  - How hormone replacement therapy affects the bones, heart, and vascular system of older women.
  - Hormone replacement therapy in postmenopausal women and the recommended dosage levels and types.
  - The role of body fat, fat distribution, and female hormones in diseases common in older women.
  - Why women appear to be less successful at quitting smoking than men, the benefits of smoking cessation in women, and how much time is required after smoking cessation to reduce the health risks in women.
  - The most important cardiovascular risk factors in women.
  - The significance of high lipid levels in women as compared with men.
  - The best drugs to use to treat coronary heart disease in women.
  - The causes and consequences of weight loss and undernutrition in older women.
  - What constitutes a healthy diet for an older person.
  - Racial or cultural factors that contribute to weight gain in minority women, and when being overweight is detrimental to health.
  - What effects living alone has on the dietary habits of older women.
  - How a lack of family or social support systems contributes to physical and mental decline in older women.
  - The effects of widowhood on a woman's ability to function.
  - How older women cope with disability, and the resources available to them.
  - Which aspects of mental and physical decline associated with aging can be reversed.
  - What an older woman can do to preserve her ability to function well into her advanced years.
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# Cardiovascular Function and Disease

## Themes

Deaths from cardiovascular diseases (CVD) account for one-half of all deaths among women. A leading problem among CVDs is coronary heart disease (CHD), which causes 245,000 female deaths each year. Major differences exist in the seriousness of CVD among various racial and ethnic groups of women: more deaths from CVDs occur among Black women than among white women, for example, but Hispanic and Native American women have remarkably less CHD than white women.

For years, research directed at identifying and modifying risk factors for CVD, including behavioral, cultural, and socioeconomic factors, was conducted primarily among men. Yet some current research suggests that women may be different from men in terms of these factors, for instance,

in their physiologic response to stress, their increased responsiveness to behaviors that reduce risk, and their poorer compliance with postcoronary rehabilitation programs. Also, poor compliance has been noted among women on hormone replacement therapy, a potential risk modifier unique to women.

Priority topics for research include the formation of blood and other clots in the arteries, treatment for obesity, and hormone replacement therapy. Besides these topics, research on risk factors for stroke associated with women must increase. These include pregnancy, autoimmune diseases, use of oral contraceptives, migraine headaches, high blood pressure, diabetes mellitus, psychosocial factors, exercise, and nutrition.

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## The Working Group on Cardiovascular Function and Disease recommended that researchers study:

- The psychological and social factors contributing to cardiovascular disease (CVD) among women and ways they can be measured.
- The impact that CVD in an older woman has on family members.
- The best strategies to promote healthy behaviors and reduce risk of CVD in women.
- Why medical resources for testing and procedures are used less by women CVD patients and their doctors; why participation in cardiac rehabilitation programs is also low among women; and what a woman's special needs are during rehabilitation.
- Why women have poorer outcomes than men after heart attack and coronary revascularization procedures.
- How compliance with hormone replacement therapy can be improved and the full, long-term effects of this treatment.
- Whether stroke occurs differently among different age and race groupings of women, and the factors contributing to changes in incidence of stroke.
- The prevalence of peripheral artery disease and how it is related to other CVDs.
- The best, most cost-effective ways of treating hypertension in women, and the best treatments for pre-eclampsia and hypertension in pregnancy and how they can be prevented.
- The differences in CVD risk factors among women who are diabetic, the consequences of lipoprotein modifications in these women, and how the way insulin is administered affects the risk of CVD.
- Why systolic blood pressure tends to increase in postmenopausal women.

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- The effects of contraceptive use on normal and hypertensive women, and the effects of behavioral changes intended to manage hypertension.
  - What are safe, effective ways of controlling obesity, and whether low-fat diets before or at the time of menopause can lower the risk of contracting CHD.
  - The factors in the higher incidence of CHD and stroke among Black women, and the ethnic or racial differences in the way these diseases are manifested.
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# Malignancy

## Themes

Death rates for all cancer sites combined have declined somewhat since 1973 for women under age 55, in part because of major decreases in the incidence of cervical and uterine cancer. However, the number of deaths from the two most common causes of cancer death in women, breast and lung cancer, are increasing. Moreover, the death rates from these cancers, particularly lung cancer, are likely to increase substantially over the next decade. Because the largest number of cancer cases and deaths are due to cancers of the lung, breast, large bowel, and gynecological malignancies, these cancers are the priority research topics.

Lung cancer has surpassed breast cancer as the leading cause of cancer death. Lung cancer is almost entirely due to cigarette smoking.

Today's woman smoker is at greater risk of dying from a smoking-related disease than her counterpart from the early 1960s because it is likely that she began smoking at an earlier age, has more years of smoking in her lifetime, smokes more cigarettes per day, and inhales more deeply. In order to decrease smoking initiation and increase smoking cessation, research should focus on cigarette advertising, weight control, social supports, and negative affect regulation. Of special concern is the specific targeting of advertising at minority women, such as Hispanics and Blacks.

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## The Working Group on Malignancy recommended that researchers study:

- Ways to discover breast cancer before any malignant growth occurs.
- The incidence of breast cancer in relatives to see if certain women are genetically predisposed to breast cancer and, if so, how these women can be identified prior to the onset of cancer.
- What specific efforts should be directed toward women from specific racial and/or socioeconomic populations to reduce breast cancer.
- Whether familial risk for cancer can be controlled.
- Whether cancer can be prevented by following a specific diet.
- The feasibility of nonsurgical treatments for specific cancers.
- The short- and long-term benefits and risks for cancer among women taking oral contraceptives or undergoing postmenopausal hormone replacement therapy.
- Whether hormone therapies pose a greater risk to women with a history of malignancies and to women from different ethnic groups.
- The effectiveness of chemoprevention treatments for women at high risk for developing cancer.
- How to increase the use of the Papanicolaou test among underserved women in the United States, and how to make other screening methods available to them.
- How to improve screening for ovarian cancer.
- Methods for preventing recurrence of ovarian cancer among women who have recovered from ovarian cancer.
- The effectiveness of oral contraceptives in decreasing the occurrence of ovarian cancer, and whether the new low-dose preparations have this effect.
- The influence of certain sexual practices of adolescent and young adult women on their risk of cervical cancer.

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- The nature of the relationship between hormone (estrogen and progesterone) replacement therapies and the development of cancer of the uterus.
  - The symptoms of colorectal cancer, and how to prevent it.
  - The effects of active and passive smoking on women's risk for cervical cancer.
  - Effective means to discourage adolescent and young adult women from starting to smoke.
  - Social support methods for women who are quitting smoking or losing weight.
  - How to influence a woman's attitudes so that she will want to change negative or unhealthy behaviors.
  - The special needs of minority women and women of lower socioeconomic status to encourage them to not smoke or to stop smoking.
  - The reasons for smoking relapse.
  - Improved techniques for early detection of lung cancer in high-risk women who continue smoking.
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# Immune Function and Infectious Diseases

## Themes

More than 1 of every 10 people has a condition related to immunologic illnesses that often results in disability throughout life as well as a shortened life expectancy.

Several of these autoimmune diseases affect women more than men, and all of them cause increased illness in women, frequently during pregnancy: autoimmune thyroid diseases (Graves' disease and Hashimoto's disease), rheumatoid arthritis (a chronic inflammation of several joints together), systemic lupus erythematosus (an inflammatory immune disease characterized by excessive production of antibodies directed against the body's own tissues), scleroderma (a chronic disease of unknown cause characterized by overproduction of collagen), diabetes mellitus, and multiple sclerosis (a degenerative disease of the central nervous system).

All of these diseases impair function, often of the musculoskeletal system, which may then reduce mobility and the ability to perform self-care.

In the area of infectious diseases, sexually transmitted diseases (STDs) and urinary tract infections

have the greatest impact on women's health. STDs directly affect a woman's reproductive life by causing pelvic inflammatory disease, infertility, ectopic pregnancies, spontaneous abortions, prematurity, low birth weight, chorioamnionitis, congenital infections resulting in fetal loss, or mental retardation or infections in the newborn. While all women are susceptible to STDs, the incidence and prevalence of these diseases are several-fold higher in minority populations, most notably among Blacks and Hispanics who reside in the inner city.

Teenagers are at a particularly high risk because of unique biological factors, such as an immature endocrine system and behaviors, which include sexual debut and infrequent use of condoms.

Viral STDs have also become major problems, especially those caused by the human immunodeficiency virus (HIV), genital herpes simplex virus (HSV), and human papillomavirus (HPV).

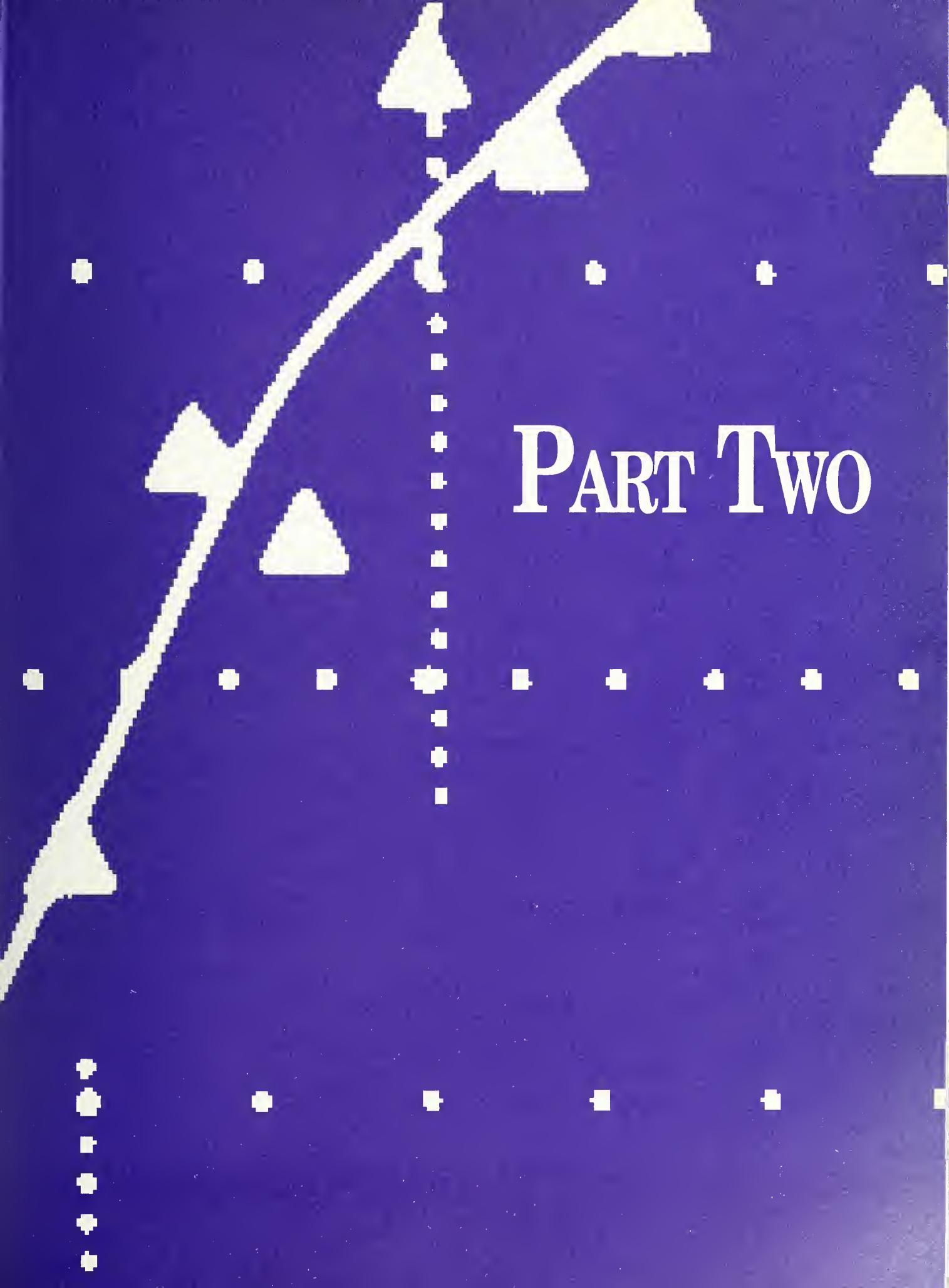
Over 19,000 cases of AIDS in women have been reported to the Centers for Disease Control.

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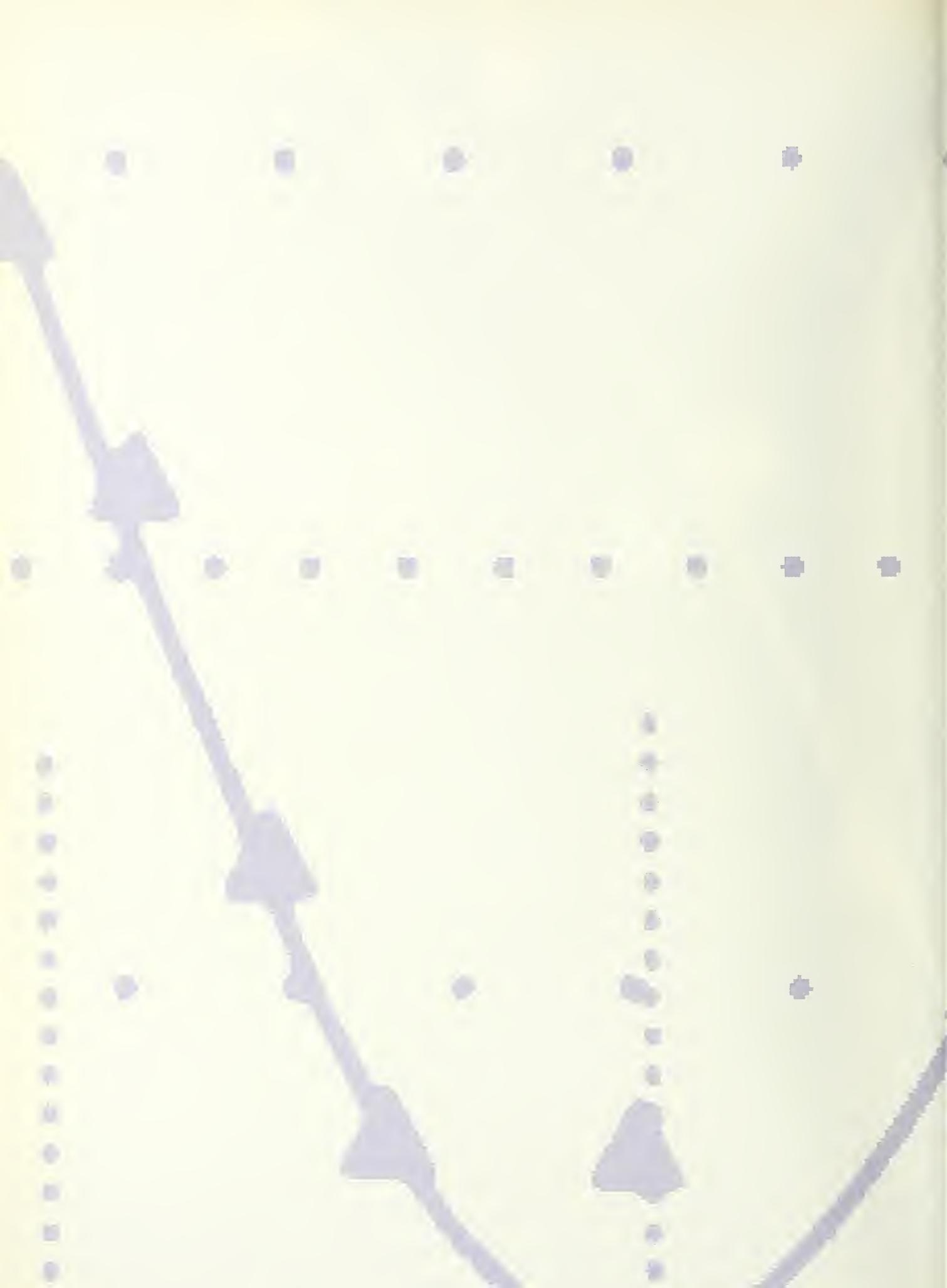
## The Working Group on Immune Function and Infectious Diseases recommended that researchers study:

- What can be done to clarify the causes of immunologic diseases.
- What makes some people more resistant or susceptible to alterations in their immune systems.
- The effect of pregnancy on the immune system.
- The causes for the differences in the immune system in some pregnant women and not others.
- The reasons women of different races and ethnic groups are more susceptible to inflammatory immune diseases, such as systemic lupus erythematosus, than other women.
- The long-term effects that drugs prescribed for immune diseases have on infertility, osteoporosis, coronary artery disease, and pregnancy.
- How immune diseases can best be treated during pregnancy.
- The relationship of the immune system, if any, to the incidence of sexually transmitted diseases.
- The relationship of the immune system to a susceptibility among women to urinary tract infections.
- The relationship of sexually transmitted disease infections and AIDS.

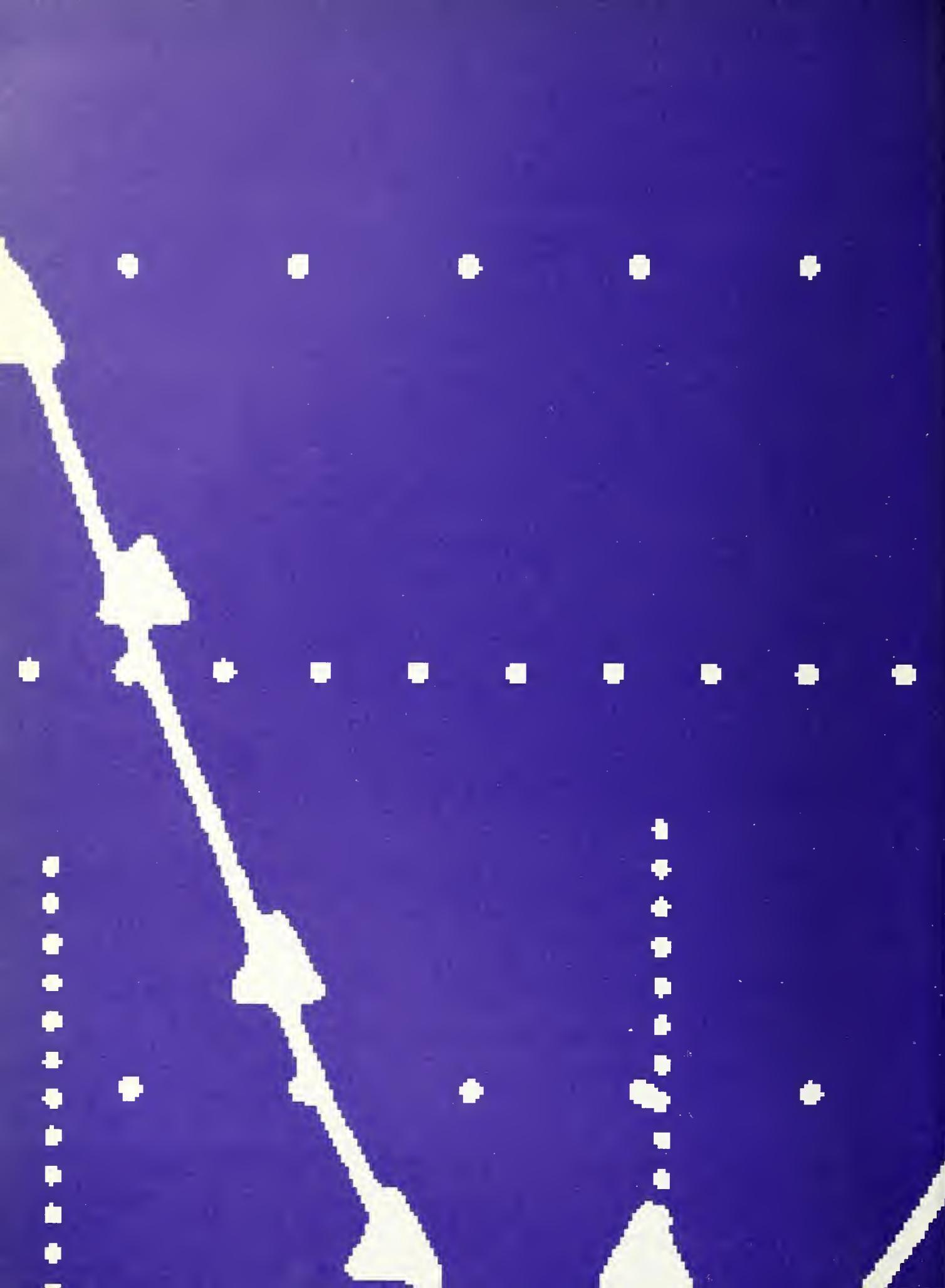
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- The role of HPV in the development of cervical cancer.
  - Development of vaccines to prevent infections caused by sexually transmitted diseases and HIV infections.
  - The prevention of interstitial cystitis.
  - The factors that cause urinary incontinence in some women and not others.
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## PART TWO



# OVERVIEW



# OVERVIEW

*Prepared by Workshop Cochairs*

*William R. Hazzard, M.D., Professor and Chairman, Department of Internal Medicine and Director, J. Paul Stricht Center on Aging, Wake Forest University Bowman Gray School of Medicine, and Mary Lake Polan, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, Stanford University School of Medicine*

The Workshop on Opportunities for Research on Women's Health, sponsored by the Office of Research on Women's Health (ORWH) of the National Institutes of Health (NIH), was held in Hunt Valley, Maryland, September 4-6, 1991. The workshop was preceded by an extensive planning process that involved input from leaders in the academic and scientific research communities as well as public testimony from advocacy groups that focus on a broad agenda of concerns related to women's health. The workshop design that resulted from the planning effort was unique, and the report which follows reflects this design. The opportunities for research on women's health were evaluated from a two-dimensional perspective: the first approach was developmental and provided for an examination of four segments of the life span of a woman: birth to young adulthood (0 to 15 years of age), young adulthood to perimenopausal years (15 to 45 years of age), perimenopausal to mature years (45 to 64 years of age), and the mature years (ages 65 years and older). The second dimension consisted of a crosscutting examination of six scientific areas—some broadly physiological and others oriented more toward particular diseases—with special reference to women's health. These areas

are reproductive biology, early developmental biology, aging processes, cardiovascular function and disease, malignancy, and immune function and infectious diseases.

Participants in the workshop were selected on the basis of their particular expertise across a broad range of specialties, from molecular biology through population-based research and from conception and intrauterine development through aging and old age. Also included were experts from fields related to the utility and cost-effectiveness of biomedical research—for example, economics and behavioral science. All participants were assigned to both a Life Span and a Crosscutting Science working group.

What follows in this report is a highly distilled, yet broadly ecumenical, research agenda. As a consequence of the workshop design, the agenda includes a somewhat redundant list of research priorities and recommendations. This overview highlights some of the most urgent issues for research on women's health today, as well as several areas that seem to offer rare opportunities for fruitful research on behalf of women. (A com-

prehensive list of recommendations for research appears in the working group reports that follow.)

## *Overall Themes*

One key theme emerged from the deliberations of both the Life Span and Crosscutting Science working groups: neither behavioral scientists nor those in basic research can, in isolation, adequately address the vast array of issues in women's health. For example, the behavioral and social context in which women lead their daily lives must serve as a subject for research. In addition, the variables that define this context must be built into the design of any research study for which there is a reasonable presumption, based on prior knowledge, that such variables will be important to the outcome of the study. Research into what works best for primary and secondary prevention of cardiovascular disease in women can serve as one example of the type of studies for which it is reasonable to assume that social and behavioral variables will be inextricably bound together with biology.

A general overview of some of the elements to be considered in shifting the emphasis to accommodate the behavioral, social, and racial/ethnic factors in women's lives include the following:

- Investigation of the full range of special issues that relate to the socioeconomic status and ethnic background of various subgroups of women.
- Support of interdisciplinary research that draws upon the expertise both of behavioral and biomedical scientists in the design of research protocols that can provide full answers to basic scientific, clinical, and epidemiologic questions.
- Emphasis in the research agenda on prevention—without undermining the emphasis on the ultimate goal of curing disease. Prevention strategies have the best chance of succeeding if behavioral and biomedical scientists collaborate. Only in this way can the proposed research strategies accommodate the full diversity of socioeconomic and racial/ethnic groups in the Nation.

Workshop participants also were concerned that information related to women's health problems has been limited because women—especially women of childbearing age—are frequently excluded from clinical trials. In addition, participants stressed that, in future studies, women scientists must be included at all stages of the study design: from the inception through design, and process of clinical studies. Participants noted that there is another reason why there are relatively fewer data on women's health; right now, there are very few women in any of the decision-making roles in biomedical research and clinical medicine. However, there are workable remedies for this situation. For instance, the traditional university tenure system compels many women to forgo family life; an alternative approach is to provide for appointments that undergo regular review. These issues and alternatives are addressed in more detail in subsequent sections on women as research subjects and careers for women in biomedical research.

## *Selection of Research Recommendations*

The research recommendations in this report can be grouped into three classifications of women's health issues. First, the workshop participants considered a cluster of questions arising from the fact that some health problems afflicting both genders have been studied primarily in males (in many instances, the diseases are more prevalent, or have particularly adverse outcomes, in males). These illnesses may manifest themselves differently in women than in men, or they may have quite distinct causes. Some examples are injuries, substance abuse, AIDS, lung cancer, and coronary artery disease.

Second, the roster includes health problems that are more prevalent in women, although not unique to them—rheumatoid arthritis and diabetes mellitus are two notable examples. Frequently, these illnesses, although not fatal in themselves, take a heavy toll on women's lives. In extreme cases, they can lead to disability and a need for nursing home care. Some of these conditions—such as con-

genital dislocation of the hip and scoliosis—are relatively rare, while others, such as autoimmune disorders and osteoporosis, are more common.

Third, a heterogeneous group of problems has been identified that disproportionately affects women in families: developmental disabilities in children, problems of children and the family, sexual activity among adolescent girls, sexually transmitted diseases (STDs), fertility and contraception, and violence and sexual abuse. Many health problems affect only women: breast cancer (nearly unique to women), uterine cancer, ovarian cancer, cervical cancer, endometriosis, female infertility, and menopausal symptoms and sequelae.

Several high-priority and special-opportunity items on the research agenda deserve special mention. First, developmental and reproductive biology, in conjunction with studies of the life span period between birth and young adulthood, offer a particularly exciting and appealing focus for research. Such studies can take advantage of cutting-edge technology to chronicle the events that characterize the normal physiology of development and reproduction, as well as the most significant events between birth and about 15 years of age. Similarly, these techniques can provide significant new insights into what has gone awry in abnormal development. Advances in molecular biology and genetics, as well as sophisticated laboratory and animal-based research, suggest that these areas, relatively neglected in recent decades, are ripe for major breakthroughs.

Second, the full range of effects of estrogen deficiency following menopause must be thoroughly documented. We still do not know precisely what occurs throughout the various systems of a woman's body after the sharp decline in levels of female hormones that accompanies menopause. Nor have researchers assessed the full potential of estrogen replacement (used as prevention or therapy) to correct the problems that can accompany menopause, such as the onset of heart disease. Finally, women need clear and unequivocal answers to lingering questions about the safety of using replacement estrogen. Is there, for example,

a significant link between the use of estrogen in postmenopausal women and the development of breast cancer?

Third, research is crucially needed regarding two mental health problems that are especially onerous for women: depression and dementia. To yield results that will be genuinely useful to women, studies on depression and dementia must shift in emphasis to a more considered integration of both the behavioral and biological factors at work in these illnesses. Another high priority on the research agenda is to study factors that culminate in disability and that arise from the multiplicity of disease- and time-related processes to which women, given their greater longevity, are uniquely vulnerable. In order to clarify all that is involved in their onset and possible therapy, research on depression, dementia, and disability has to be highly sophisticated, taking into account a full range of issues, including social and economic status as well as racial/ethnic variables that together lead to these debilitating conditions. If we could learn more about these three conditions, the benefits for women throughout their lives would be tremendous. Because they imply such frightening outcomes as social isolation and dependency, the probable consequences of depression, dementia, and disability are singularly disturbing to women and give rise to considerable anxiety.

## ***Life Span Working Groups***

### **Birth to Young Adulthood**

Several basic questions must be studied covering birth to young adulthood in a woman's life, notably, the biologic differences between males and females and the ways that these biologic differences affect patterns of normal development across racial and ethnic groups. The research agenda also should include studies on abnormalities in genetic development that may occur in females and their impact on later life. More research is needed on the biological basis for differentiation of sex within the fetus in utero and for sex differences among newborns, as well as on survival and growth rates for females. Racial and

ethnic variations in survival rates also deserve special attention.

Because a mother's health is so important to the health of her children, research on the safest and most effective treatments for preexisting disease during pregnancy and the impact of these treatments on the fetus are mandatory. Specifically, researchers need to develop noninvasive diagnostic techniques for monitoring fetal well-being and growth, as well as new therapeutic interventions to prevent low-birth-weight babies.

Much more needs to be known about the normal physical and physiological development of girls. This work will help greatly in determining the factors that may predispose girls to specific diseases—or to risk-taking behavior—and, conversely, the factors that promote physical and emotional strength in girls. Longitudinal studies of females throughout the life cycle, begun in early childhood and adolescence, can provide baseline data for later assessments, as well as define the elements of normal health of girls and of women. These studies also will furnish important insights for developing successful prevention strategies so that some of the health problems that now burden women can be prevented while women are still young.

## Young Adulthood to Perimenopausal Years

During the young adult years, a woman's well-being is intimately connected with her ability to live free of problems associated with sexual function, STDs, control of fertility, pregnancy, and childbirth. Research into every aspect of female reproduction is mandatory. In particular, women need more options for contraception that are safe and reliable so that they are free to choose for themselves the timing and frequency of pregnancy. Also vital is research into the linkage between reproductive diseases and infertility. Endometriosis and uterine leiomyomata, in particular, often necessitate the drastic remedy of a hysterectomy. In addition, researchers need to find specific answers to a broad range of questions about the causes and possible means of preventing the biologic antecedents of infertility and repeated miscarriage of fetuses, including pre-

term delivery. Investigation into other complications of pregnancy—notably the hypertensive disorders of pregnancy, premature rupture of the amniotic membrane, and intrauterine growth retardation—is crucially needed as well.

Cancer is the leading cause of death among women between the ages of 15 and 44. Research is needed to discover improved ways to detect breast and genital cancer earlier and to develop more effective therapies for these malignancies. Further, the widespread morbidity associated with hormonally related illnesses, such as endometriosis and chronic lack of ovulation, requires an initiative that includes both basic cellular and epidemiologic studies and considers possible differences among women from various ethnic and socioeconomic backgrounds as well.

STDs, including HIV infection, require an immediate and concentrated research effort. In many ways, women are affected more severely by these conditions than are men, and it is more difficult to detect many of the STDs in women. As a consequence of STDs, women may suffer from infertility, tubal pregnancy, genital cancer, early fetal loss, and congenital or perinatal infection. The infant born to a woman with an STD is also more likely to be of low birth weight. We need to know more about the basic biology of the infection and the cellular response to STDs, as well as the socio-economic and behavioral risk factors for these infections.

The physical and psychosocial traumas that can occur in women between the ages of 15 and 45 (including depression, physical injuries, and substance abuse) reflect the social turbulence common among this age group. To achieve a full understanding of these problems and what causes them, sociologic and epidemiologic studies will be necessary to determine the particular factors that place women at risk.

## Perimenopausal to Mature Years

Studies on the effects of estrogen levels on health lead the list of recommendations for improving the health of women in their perimenopausal to mature years. The results of clinical trials related

to primary and secondary prevention can specify the long-term risks (e.g., for breast cancer) versus the benefits of estrogen use in postmenopausal women. In addition, clinical trials results can provide firm data on the effects of estrogen in preventing osteoporosis and its attendant fractures, on heart disease and gynecologic cancers, and on improving cognitive function and overall quality of life. These investigations should be coupled with more basic research into the effects of estrogens or progestins, singly or in combination, in modulating cellular and tissue function, especially in key target organs. Other studies are needed to develop alternatives to estrogen use for treatment of perimenopausal symptoms and for prevention of heart disease and osteoporosis in those women who cannot safely use estrogen itself.

A second area of emphasis for researchers is the behavior and health in the women in perimenopausal to mature ages. The particular stressors that most influence women's health during these years need to be identified. Successful interventions for long-term weight management, including strategies for increasing levels of physical activity, are vital, as are investigations for identifying and controlling risk factors for cardiovascular disease in women. In particular, studies should clarify which of the several parameters regarding lipid levels serve as the best indicators of high risk for cardiovascular disease in women.

## Mature Years

In concert with the Perimenopausal to Mature Years Working Group, the Mature Years Working Group recommends that studies on the long-term effects of menopausal changes, with special reference to estrogen deficiency, be an important priority.

The causes and effects of disability, which is a final common pathway leading to dependence, dysfunction, and eventual death in aging women, must be the focus of more intensive research. Longitudinal and cross-sectional studies are needed to elucidate all of the precipitating factors that cause disability and its consequences in women. It is also important to learn how a woman's perception of herself as a disabled person might influence

the way she uses the health care system and her willingness to follow professional advice about her health. The possible role of interventions—such as physical activity—for disabled women as they resume daily activities should be explored as well.

As a general consideration, researchers must determine why older women are less likely to avail themselves of health behaviors that prevent disease and disability than are younger women and to learn the best means to motivate women who are over 65 and in the various racial and ethnic groups to adopt these behaviors. Also, it is crucial to gain some understanding of how older women interact with the health care system by examining the role of physical barriers, cultural and educational barriers, possible denial of illness, and fear of institutionalization, among other factors. In order to study the ways that older women relate to the health care system, researchers need to find better data bases and information sources that capture relevant information.

## *Crosscutting Science Working Groups*

### Early Developmental Biology

The primary goal of the research initiatives recommended by the working group on Early Developmental Biology is an understanding of the basic scientific foundations of normal embryonic development as it relates to the possible clinical problems of pregnancy. Recent innovations in molecular genetics have facilitated studies into the activation of sequential genes during the production of sperm and ova and investigations into the ways that this series of steps differs in males and females. Also, understanding the immunologic and endocrine interactions involved in implantation of a fertilized ovum requires a major research initiative, as does a more focused study on the development of the placenta and the transport function by which it nourishes the infant.

Fetal differentiation—as it proceeds at the cellular level and leads to the development of individual organs—provides an important focus for research. A detailed picture of energy metabolism

and growth in the fetus is needed as well. This is an opportune time for these studies because of the recent explosion in knowledge about a broad range of growth factors. Basic research in this area can provide important clues for devising interventions to prevent intrauterine growth retardation.

In some cases, intrauterine growth retardation contributes to loss of a fetus or neonatal death, or it can result in subnormal development during the infant's early years. Studies are needed to clarify the consequences of maternal diseases, such as pregnancy-induced hypertension and diabetes mellitus on intrauterine growth. Studies on the immunologic abnormalities that lead to repeated miscarriages are crucial as well. Other investigations of high priority should focus on the social and demographic factors that influence decision-making by women regarding adequate prenatal care or persistence in substance abuse. There are also important gaps in knowledge concerning the relationship between these behaviors and the subsequent birth of premature infants. More complete knowledge about the biochemical basis of normal birth is critical for developing strategies to prevent preterm birth.

New methods are needed to detect and monitor genetic and growth abnormalities in the fetus, especially since many fetuses are affected adversely by factors such as inherited traits, environmental toxins, and substance abuse.

## **Reproductive Biology**

New research initiatives on fertility and contraception are needed. Significant progress in these areas requires a larger research investment to define, in the reproductive process, new targets of vulnerability within the various sites in the body that play a role—the central nervous system, the immune system, and the reproductive organs. Since proper reproductive function depends on the interaction between the central nervous system and the ovary and uterus, studies must be directed at the hypothalamic and pituitary control of these physiologic processes.

The ovary produces the female gametes and also secretes the female sex hormones, estrogen and progesterone. More research is needed on the biology of the ovary and on the full spectrum of its functions, including its role in the reproductive process and in calcium and lipid metabolism. Diseases of the ovary, such as polycystic ovary syndrome and ovarian failure, deserve focused investigation.

The biology of behavior, and in particular the link between reproductive and mental health, need to be fully explored. Specifically, the effects of reproductive hormones must be addressed because of a possible relationship between ovarian hormones and affective disorders in women with poorly understood mood swings. Postpartum and postmenopausal women with hormonal deficits may also experience negative emotions and show unexplained changes in behavior as a result of alterations in hormone levels. These phenomena, too, need to be better understood.

## **Aging Processes**

Many important research recommendations concern the physical aspects of aging in women. More research is needed on aspects of aging at the cellular and subcellular levels. The various phenomena of aging also need to be investigated in regard to significant differences among diverse populations, with special attention to consequences of aging that most affect older women, such as disability and dependency. The genetic determinants of longevity in women need to be identified, along with the role of genetic factors in the senescence of the immune system.

It is important to learn more about the causes and consequences of chronic conditions in women as they age, including studies on the ramifications of sequential development of these conditions. Those chronic conditions that predominantly affect women—such as osteoporosis—require further study to determine the extent to which these are the unavoidable result of aging as opposed to consequences of inheritance, other diseases, or health-related behaviors.

Issues related to cognitive function and the special risk of Alzheimer's disease for women require intensive study; both basic and applied research are necessary. To provide baseline data for this work, studies are needed to trace the natural history of functional decline—or improvement—with age and also to learn whether changes in cognitive function differ across populations.

It is necessary to know why, and how, the manifestations and clinical course of heart disease differ in men and women. Studies are required to examine the reasons why women may be less successful at altering risk factors for heart disease, why triglyceride levels are better predictors of coronary risk in postmenopausal women than men of comparable age, and why diabetes is such a powerful risk factor for atherosclerosis in women.

More research is needed to understand the interplay among factors that cause women to neglect their diets, addressing psychosocial factors and overall health status.

Disability is a focus of special concern for women as they age. Research in this area should focus on appropriate measurements of disability in women; on factors that lead to disability versus maintenance of function; and on the several dimensions of social, physical, and psychological homeostasis that are related to disability. It is necessary to know how to prevent disability, in both the short and long term.

## **Cardiovascular Function and Disease**

Cardiovascular disease is the major cause of death for women, as for men, although it occurs in women, on the average, about 10 years later in life than it does in men. Many of the research recommendations from the Cardiovascular Function and Disease Working Group concern the benefits and risks of postmenopausal sex steroid replacement. This area is seen as a key area for research. Studies should include not only the large-scale, multidimensional trials mentioned above (and included under the broad umbrella of the NIH's Women's Health Initiative), but also secondary prevention trials of

estrogen replacement in women who have coronary heart disease.

The predictors and parameters of clinical cardiovascular disease in women must be identified, including the range of unusual presentations and of the pathophysiology of coronary artery disease, stroke, peripheral vascular disease, hypertension, and sudden cardiac death. More information about the reasons for observed differences in health care utilization by women who need care for cardiovascular diseases is required as well.

Diabetes mellitus and its particularly adverse impact on the health of women is another area with important opportunities for research. Hyperinsulinemia, related obesity, hypertension, dyslipoproteinemia, and the mechanisms related to these abnormalities at the cellular and physiological level deserve high priority on the research agenda. Investigators also need to learn whether there are gender-related differences in how the disease progresses and what the best choice of therapy is for two other related conditions, thrombosis and thrombolysis. Finally, the particulars of the relationship between exercise and obesity in women merit thorough research.

## **Malignancy**

The highest priority for research on malignancies in women is breast cancer because this disease is so prevalent and so deadly. Studies should encompass research on genes and nucleic acids, on the development of methods for early detection, on clinical trials, and on strategies for prevention. As noted by several other working groups, the trade-offs regarding the role of estrogen (with or without progestin) in postmenopausal sex steroid replacement require careful examination in the context of both broad-based clinical trials and those focused specifically on breast cancer.

Gynecologic tumors constitute a second area of high priority. Cervical cancer, and the special role of the human papillomavirus in its genesis, must be more fully investigated. Questions pertaining to uterine cancer—particularly the exact nature of the relationship between estrogen and progestin replacement and risk—are of extreme importance.

Ovarian cancer also must receive more intensive attention. Present physical examination and imaging techniques make it impossible to diagnose this type of cancer until the disease is quite advanced. Researchers need to find a serologic marker that will permit detection of ovarian cancer as soon as possible after the disease process has begun. The precise balance among the trade-offs regarding the possible role of estrogen and of oral contraceptives as well as the etiology of—as opposed to possible protection from—this malignancy require thorough examination.

At present, there are special opportunities for research on colorectal cancer. The specific genetic precursors for this malignancy as it occurs in women, as well as the role of diet (notably, high-fat, low-fiber) represent important areas for research that utilizes current knowledge and techniques.

Finally, lung cancer and the specific issues germane to tobacco smoking are of critical importance for women. In recent years, the incidence and mortality of lung cancer among women has risen dramatically and focused considerable attention on this public health problem. Particular areas for concentrated research include the pharmacologic (addicting) effects of nicotine, weight gain after cessation of smoking, the need for social support in cessation efforts, and practical issues related to preventing the onset of smoking, particularly among young women.

Issues of access by women from various underserved populations to prevention screening (most notably, the Papanicolaou test) are also in need of illuminating research.

## Immune Function and Infectious Diseases

Two major categories of disease were considered by the Immune Function and Infectious Diseases Working Group: those involving apparent aberrations of the immune system—including autoimmune diseases such as systemic lupus erythematosus (SLE), thyroid disease, and scleroderma and the infectious diseases that primarily affect women.

Specific research initiatives should be developed to understand the etiology and pathogenesis of immune diseases that are not now curable because this knowledge may facilitate development of better treatments. Research should focus on the cellular mechanisms of immune function and antigen presentation as well as on the relationship among immune cells, their secretory products, and the surrounding tissues with which they interact. These interactions are especially important in pregnancy, since immunologic function is altered such that changes in autoimmune disease states are a possible consequence. Furthermore, the consequences of implantable biomaterials, such as temporomandibular joint implants, must be thoroughly investigated.

Population-based studies to determine the epidemiology and natural history of immunologic diseases are also crucial, in part because these diseases can lead to severe disability for women. Recently, several new therapeutic agents have become available that can mitigate the course of these illnesses, a success that should serve to stimulate much more work in this most important area.

The major impact of STDs and urinary tract infections on the lives of women dictates that these be established as high priorities for future research. In addition, basic research is needed to describe the relationship of the mucosal lining of the female genital tract and its relationship to viral and bacterial infection. Because the immune response is important to the clinical consequence of many STDs, including AIDS, basic research into the microbiology, immunobiology, and pathogenesis of pathogens such as *Neisseria gonorrhoeae*, HIV, and herpes are critical.

To understand and prevent STDs, epidemiologic studies are crucial to identifying the social as well as physical factors that place some women at high risk for these diseases. In addition, clinical studies, both diagnostic and therapeutic, are needed to elucidate better ways to detect these illnesses and to develop more effective treatments.

Because there is a tremendous behavioral component in the development of STDs, collaborative studies on specific behavioral research and the

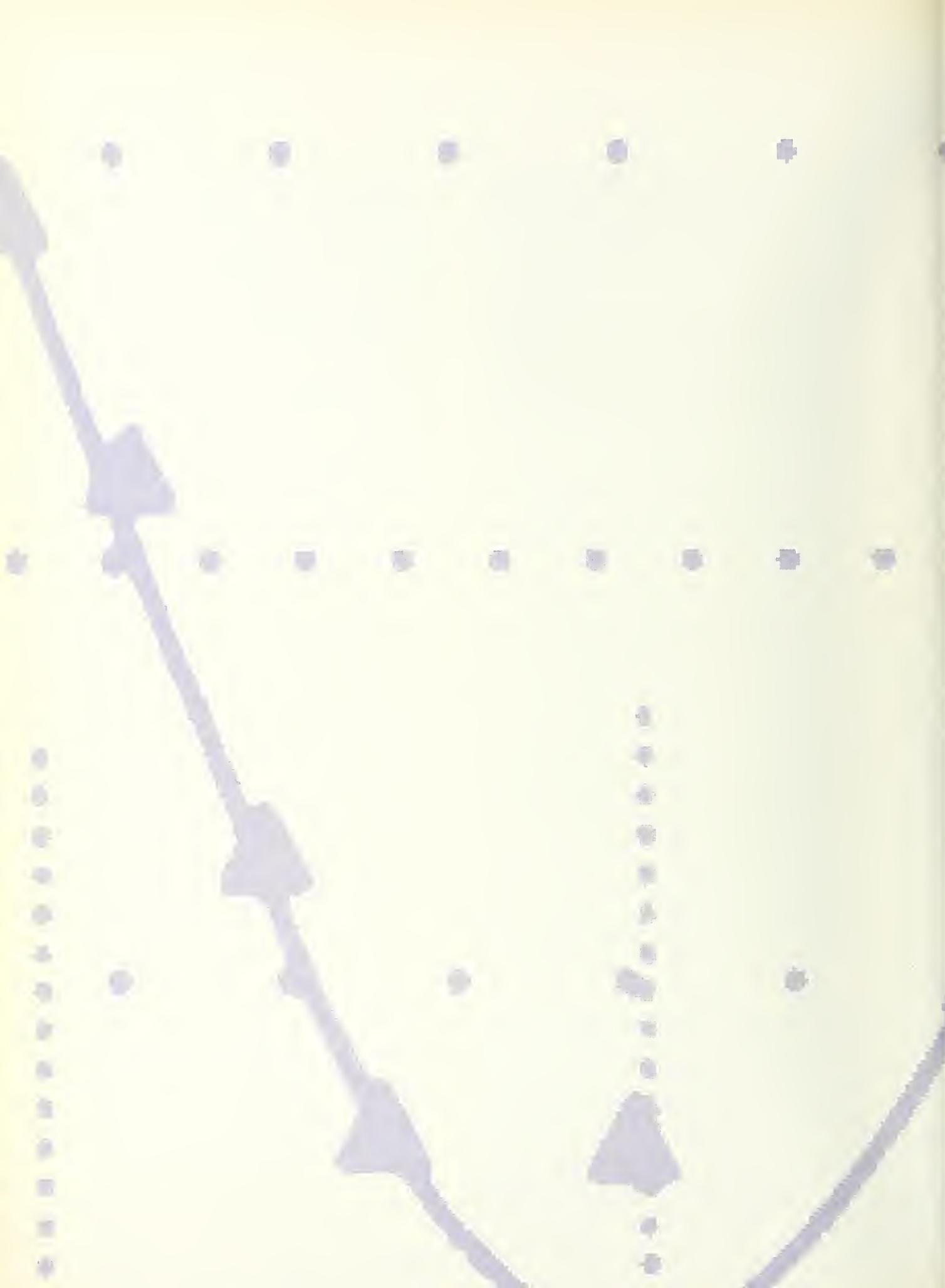
effect of education as a prime and effective intervention are critical. Carefully formulated studies to document this effect and to extend the therapeutic benefit of educational protocols are required.

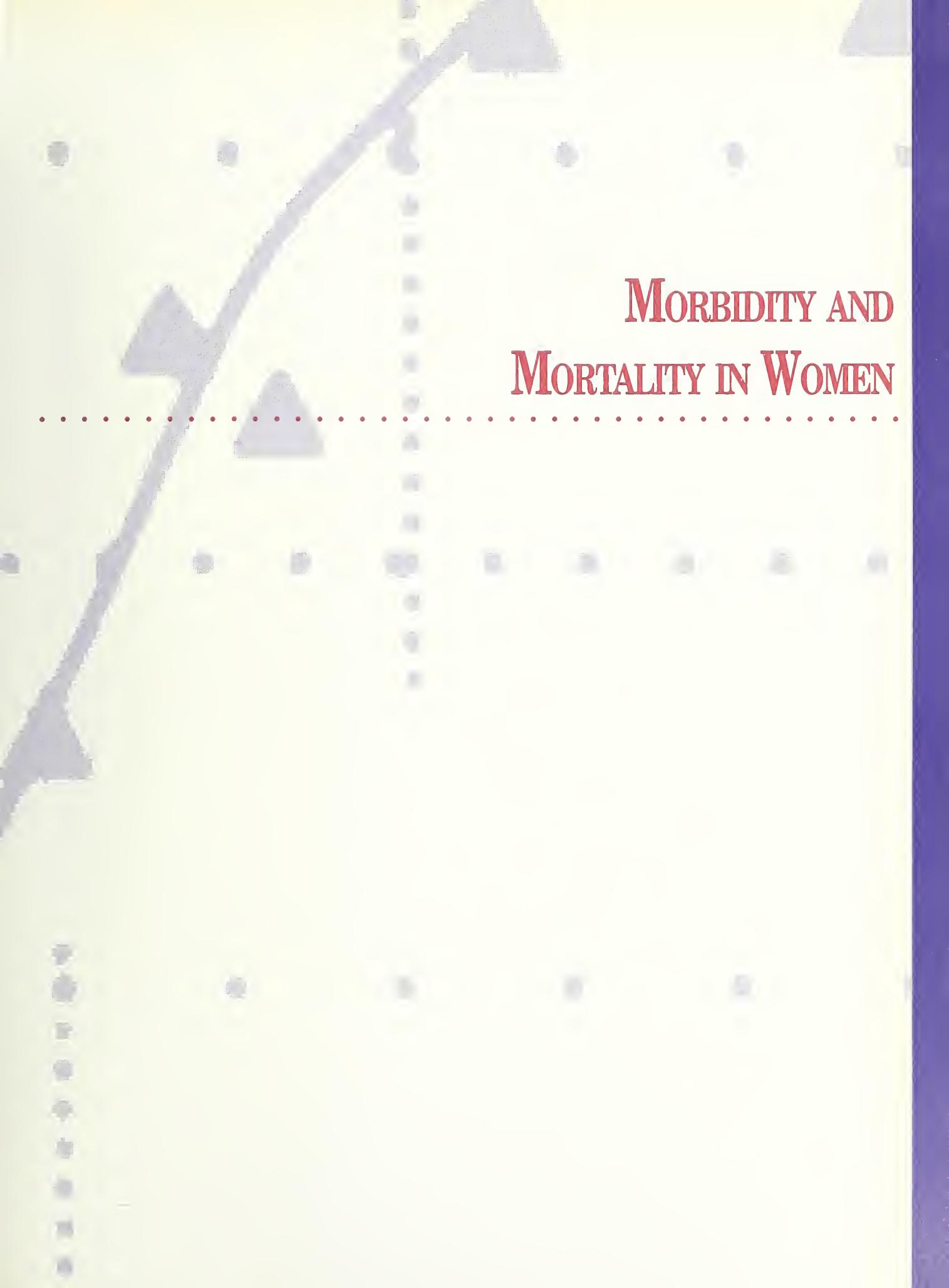
## **Conclusion**

The research agenda outlined at the Workshop on Opportunities for Research on Women's Health provides the comprehensive framework, along with the specific research priorities, by which the NIH can accomplish its most important mandate to advance the health of all women.

Together, the overriding themes of interdisciplinary research; increased interaction among behavioral, basic, and clinical scientists; and the close associa-

tion between basic biological questions and those regarding disease states the imply that a new way of conducting research may be necessary: broader approaches to interdisciplinary research might be stimulated by innovative mechanisms and requirements in the funding of research. Through these kinds of research initiatives, baseline epidemiologic information on women's health status can be acquired and assessed and basic biological questions can be raised and answered. The fruits of this work will result in longer, healthier, and more productive lives for women in the United States. This goal is eminently worthy of the whole hearted commitment of the research community and the NIH, together they can ensure that the research agenda detailed here will prosper.





# MORBIDITY AND MORTALITY IN WOMEN

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# MORBIDITY AND MORTALITY IN WOMEN

*This synopsis is based on the presentations by Maureen Henderson, M.D., Professor of Epidemiology and Medicine, University of Washington and Head, Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center, Seattle, Washington, and Jean A. King, Ph.D., Department of Psychology, Emory University, Atlanta, Georgia.*

The statistics on morbidity and mortality in women present a rather striking paradox. On the one hand, women live longer than men. On the other, measurements of the quality of a woman's life—in both medical and behavioral parameters—lags behind those for men. If statistics are correct, women's lives are more frequently burdened with acute symptoms, chronic conditions, and short- and long-term disabilities arising from health problems than are the lives of men.

In addition, the women of America are now facing new challenges to their health status. Early in this century, heart disease surpassed infectious diseases as the leading killer of women of all ages, and it remains so. However, among women ages 35 to 54, cancer has emerged as the leading cause of death—due, in part, to the rise in the incidence of lung cancer. The occurrence of lung cancer has increased because so many women have become regular smokers during the past 30 years.

Other social changes have had a major effect on the health of women in the United States. The sexual liberation that began in the 1960s has led to a host of new health problems, especially for

women. American girls are becoming sexually active at younger ages, leading to the growing problem of teen pregnancies. Sexually transmitted diseases such as chlamydia infection are also on the rise.

Still unknown are the full ramifications of the progressing industrial emancipation of women that has women leaving their homes and the stereotypical occupations of prior years for the potential stresses of the workplace. A popular hypothesis of the 1970s posited that the indices of women's health would deteriorate as they gave up the supposedly sheltering environments of their homes. To date, the data do not appear to substantiate this theory. Nonetheless, it is still impossible to make generalizations about the effects of women's massive entry into the workplace. Important questions persist; for example, have women been exposed to additional health hazards by leaving the home? It may take many cohorts to complete a full quota of information on women's working and retiring years before research can begin to assess the true impact of this major social change.

One trend that will have an enormous effect soon on both men and women is the overall aging of

the U.S. population. This trend has been observed throughout this century. In the early 1900s, it was primarily a consequence of lower fertility rates; in recent decades, a major decline in mortality, especially among the older age groups, has been the principal causative factor. In 1900, only 4.0 percent of the population was age 65 and over, and only 0.2 percent was 85 and older. By 1985, the percentages had risen sharply, to 12.0 and 1.1, respectively.

A development of special importance for the health of U.S. women, derived from census data,<sup>1</sup> is that the percentage of the group over age 65 that is female increased from 49.5 percent in 1900 to 59.7 percent in 1980. Even more dramatic

***"As a woman advances in age, cataracts, fractures, osteoarthritis, peripheral vascular disease, congestive heart failure, and ultimately the senile dementias slowly and inexorably destroy her capabilities to cope—and her quality of life comes to a crashing halt."***

Mary Jane Jesse, Associate Senior Vice President and Associate Provost for Health Education, University of Cincinnati Medical Center

changes were noted among the group over age 85, the so-called "old-old." Women made up 55.6 percent of this group in 1900; by 1980, they comprised 69.6 percent of those over 85. These statistics imply that women will be facing in increasing numbers the problems that may accompany old age, such as osteoporosis and Alzheimer's disease. Even now, many more women than men require care in a nursing home or personal care facility: female residents outnumber their male counterparts by nearly three to one (983,900 women versus 334,400 men in 1985<sup>2</sup>).

Finally, perceptions on morbidity and mortality among women in the United States have shifted significantly in recent years as both researchers and society have come to appreciate more fully the multitude of racial and ethnically based differences in the health status of the Nation's women. Increasing numbers of biomedical research studies are including variables that seek to elucidate the diversity in health measurements among U.S. women and its potential consequences, an important consideration for acquiring a complete picture of women's health status.

## ***Mortality Statistics***

The progress made against the diseases that most affected women prior to 1900 (notably, infectious diseases) has resulted in the longer lives that women now enjoy. Since the early years of this century, advances have been made against many conditions that principally affect women. Use of the Papanicolaou test, for example, has helped to detect cervical cancer before it becomes clinically evident, thereby improving survival rates.

Considering all races, life expectancy for males in 1900 was 46.3 years; for women, it was slightly greater, 48.3 years.<sup>2</sup> By 1980, men could expect to live nearly 24 years longer than their earlier projection (to 70.0 years), but the increase in women's life expectancy outpaced that of men: they could reasonably expect to reach age 77.4. The most recently available data, from 1988, show that this gap between men's and women's life expectancy has persisted; whereas the life expectancy for men in 1988 was 71.5 years, for women it was 78.3 years.

For Black men and women, however, the data for 1900 reveal significant differences from those for whites: life expectancy for Black males was 32.5 years; for Black females, it was 33.5 years. In 1980, although life expectancies for both Black males and females remained less than for their white counterparts, the gap between Black men and women in years of expected life was nearly the same as for whites (63.8 years for Black men; 72.5 years for Black women). By 1980, Blacks had

posted slight gains: life expectancy was 64.9 years for Black men and 73.4 years for Black women.

From birth onward, women have lower death rates than men. Specific factors may be responsible for the significantly longer life span of women. These factors, which are assumed to be biologic, are present before puberty and continue after menopause and therefore are probably mediated through a number of factors other than the reproductive hormones that are predominant during the reproductive years.<sup>1</sup> The existence of a biologic component that persists through serial social and lifestyle changes has been hypothesized as independent of race or ethnic background, but the extent of its variability among these groups and the causes of potential variability are not well known.

## Causes of Death

Among all women under age 65, the six leading causes of death as of 1988 were: heart diseases, cancer, cerebrovascular diseases, accidents, sui-

cide, and AIDS (Table 1). Five of the six causes are the same for Black women.<sup>2</sup> They are heart diseases, cancer (lung, breast, and colon cancer, in particular), cerebrovascular diseases, accidents, and homicide. The rates for cardiovascular and cerebrovascular diseases, homicide, and AIDS are more than twice as high among Black women.

For Black versus white women, comparisons of age-specific death rates for three of these causes (heart diseases, cerebrovascular diseases, and homicide) show that Black women experience their highest excess rates between the ages of 25 and 44 and that, for this same age range, the excess rates of death from these causes are greater than at any subsequent age (Table 2).

Exploratory analysis of 1988-89 death rates in the State of Washington has demonstrated that such high death rates among young adult women are associated with low educational status. This association is not found among older women, and it is stronger for accidents than for any other cause of death.

**Table 1.**  
*Six Leading Causes of Years of Potential Life Lost by  
Black and White Women Before Age 65  
1988*

### Years Lost Per 100,000 Women

	Black	White	B/W Ratio
Cancer	947	822	1.15
Heart Diseases	834	341	2.45
Accidents	683	537	1.27
Homicide	494	99	4.99
Cerebrovascular Diseases	238	87	2.74
Suicide	73	131	0.56
HIV	215	24	8.96

Based on National Vital Statistics. From *Health United States 1990*.  
US DHHS pub. no. (PHS) 91-1232.

**Table 2.**  
***Black/White Ratio by Age and Cause-Specific Death Rates in Women 1988***

Age in Years	Cause of Death		
	Heart Diseases	Cerebro-vascular Diseases	Homicide
Under 1	2.38	2.93	3.92
1-4	1.86	2.33	3.94
5-14	1.43	2.00	3.88
15-24	2.59	1.83	4.46
25-34	3.38	3.31	5.80
35-44	4.06	4.02	4.56
45-54	3.08	3.09	3.08
55-64	2.21	2.86	3.40
65-74	1.62	2.11	3.91
75-84	1.25	1.37	3.30
85+	0.81	0.86	4.38

Based on National Vital Statistics.

From *Health United States 1990*. US DHHS pub. no. (PHS) 91-1232.

Other less common causes of death before age 65 are influenza, chronic liver disease and cirrhosis, and diabetes mellitus. These conditions occur more than twice as frequently among Black women as among white women.

Leading causes of death among women age 65 and older continue to be cerebrovascular diseases and cancer. Cancers of the lung, breast, and colon remain important, but ischemic heart disease becomes relatively more important compared with other types of heart disease. Up to age 85, death rates resulting from heart disease are higher among Black women. For women over age 65, death rates for lung and breast cancers are

higher among white women than for Black women.

Specific death rates for the three leading causes of death among women for selected age cohorts are shown in Table 3.

### ***Statistics on Women's Health: Highlights***

A few of the more important statistics on women's health and, in particular, several of the more striking trends are noted here:

- The death rate from breast cancer increased 24 percent between 1979 and 1986. One in nine women can now expect to develop breast cancer in her lifetime; in 1961, the ratio was 1 in 20.<sup>3</sup>
- It has been estimated that approximately 20,500 American women will be diagnosed in 1991 with ovarian cancer.<sup>3</sup>
- Half of all women over age 45, and 90 percent of women over age 75, suffer from osteoporosis, which results in at least 1.3 million fractures in the United States each year. The major sites of fracture each year are the hip (nearly 250,000 fractures), wrist (over 170,000), and spine (about 500,000). Overall, nearly one-third of women over 65 years of age will have one or more vertebral fractures. There is an overall 12 to 20 percent reduction in survival in the 6 months after a hip fracture; and 50 percent of those who survive hip fractures require some help with daily living activities, and 15 to 25 percent need to enter a long-term care institution shortly after the fracture.<sup>3</sup>
- Heart disease is the number one killer of American women. Nearly 1 in 2 female deaths in the United States is a result of cardiovascular diseases. Women develop heart disease later in life than men. Approximately 1 in 9 women between the ages of 45 and 54 has some clinical cardiovascular disease; the rate climbs to 1 in 3 at age 65 and older. Forty-nine percent of women who have heart attacks die within a year (versus 31 percent of men).<sup>4</sup>

**Table 3.**  
**Death Rates for Three Greatest Causes**  
**of Death Among U.S. Women**  
**1988**

	<b>Rate per 100,000 Population</b>	
	<b>White Women</b>	<b>Black Women</b>
<b>Heart Diseases</b>		
15-24 years	1.7	4.4
25-34 years	3.9	13.2
35-44 years	12.5	50.8
45-54 years	54.5	167.8
55-64 years	213.3	471.4
65-74 years	656.2	1,060.0
75-84 years	2,101.5	2,625.6
85 years and older	6,597.3	5,648.1
<b>Cerebrovascular Disease</b>		
15-24 years	0.6	1.1
25-34 years	1.6	5.3
35-44 years	4.6	18.5
45-54 years	13.9	43.0
55-64 years	37.0	105.7
65-74 years	125.3	264.7
75-84 years	512.7	700.7
85 years and older	1,767.0	1,517.7
<b>Malignant Neoplasms</b>		
15-24 years	4.2	4.9
25-34 years	11.5	17.5
35-44 years	46.2	71.2
45-54 years	151.3	196.2
55-64 years	372.5	454.1
65-74 years	660.0	728.3
75-84 years	984.4	1,062.6
85 years and older	1,300.1	1,288.0

- More than 90,000 women die each year of stroke; this comprises 61 percent of all fatalities from stroke.<sup>4</sup>

### **Morbidity Statistics**

Currently available data show that, on average, women lose 15.5 years of life as a result of morbid conditions; men lose 11.5 years (Table 4). To date, it has not been possible to clearly attribute the excess morbidity in women to specific long- or short-term illnesses. Some investigators have concluded that most of this excess may simply be a consequence of the total number of years that women spend in the frail elderly condition.

It is true, however, that more women than men of every age group report or seek care for illness and disabilities, most notably for the acute conditions and short-term disability that occur during the reproductive years (18-44) and for chronic conditions and associated disability in mid- or late life. In one representative study that measured "symptomatic days" using prospective, 6-week health diaries, women ages 45-64 reported an average of 18.5 symptomatic days, whereas men noted only 11.2 such days.<sup>1</sup> Also, data from the National Health Interview Survey (NHIS) initiated in 1957 have consistently shown higher acute and chronic morbidity and higher disability days for females than for males.<sup>1</sup>

Some of the high incidence of illness experienced by women during the early adult years is to be expected because women are more likely to have greater exposure to children coming home from both day care and school with upper respiratory and common childhood infections. NHIS data from 1985 on the leading acute conditions among women and men ages 18-44 likewise show a greater incidence among women for many of these conditions. Expressed as conditions per 100 persons per year, women had 49.7 bouts of influenza versus 37.0 for men, and 30.7 common colds as compared with 21.4 for men. Acute conditions were more numerous among men than among women only in the categories related to injuries (e.g., 10.6 sprains/ strains in men versus 6.7 in women).

**Table 4.**  
***Life and Well-Life Expectancy***

Indicator	Men	Women	Difference
<b>Expectancy</b>			
Life	71.30	78.30	-7.00
Well-Life	59.78	62.70	-2.88
Difference	11.52	15.60	

Adapted from Kaplan R, Anderson JP, Wingard DL, *Health Psychology*, 1991.

## Chronic Conditions

Many of the nonfatal chronic conditions for which NHIS data are available occur more frequently in women. These differences are most apparent among persons ages 45-64. NHIS statistics for 1983-1985 (expressed as conditions per 1,000 persons, average annual rates) on nonfatal chronic conditions among this group reveal gender ratios (female/male) of 6.51 for thyroid diseases, 4.78 for anemias, 4.05 for spastic colon, 3.53 for frequent constipation, 1.64 for gallstones, and 1.59 for arthritis.<sup>1</sup>

As might be expected due to women's longer life expectancy, several of the fatal chronic conditions are less common in women. According to NHIS data from 1983-85, gender ratios (female/male) expressed as conditions per 1,000 persons for selected fatal chronic conditions for ages 45-64 are: atherosclerosis, 0.46; ischemic heart disease, 0.49; cerebrovascular disease, 0.68; and other selected heart diseases, 0.97.<sup>1</sup>

Nonetheless, gender ratios (female/male) for several other chronic diseases that are potentially fatal (calculated from unpublished data from the NHIS for 1983-85) show that women in this same age group are more likely to describe symptoms indicative of chronic bronchitis (1.96), asthma (1.41), diabetes (1.11), and high blood pressure (1.08).<sup>1</sup>

Important questions persist, however, about whether these differences in prevalence are

merely a consequence of differences between men and women in the frequency which they report symptoms. For example, physiological testing demonstrates that chronic bronchitis is more prevalent in men than in women, in contrast to the statistic above. More research must be completed before these issues can be resolved conclusively.

## Disability

In addition to higher acute and chronic morbidity prevalence rates, women report more disability days than men. Statistics divide disability into two categories: short- and long-term disability. For short-term disability, which can result from either acute or chronic conditions, women report higher rates; their activities are limited by health problems approximately 25 percent more days each year than are men's activities. Women also spend about 40 percent more days in bed, on average, compared with men. In fact, this difference in disability rates between men and women, which persists even when reproductive problems are eliminated, is greatest during women's reproductive years (ages 18-44).

In most circumstances, long-term disability is a result of chronic conditions. Women report more difficulty for all indicators of physical disability (e.g., mobility, strength, and endurance), and these gender differences tend to increase with advancing age. Also, women report that they are more likely than men at all ages to depend on others for household tasks, and to need assistance with personal care when they reach advanced ages. It should be noted that this was true only for individuals over age 80; there were no differences at ages 65-79.<sup>1</sup>

## Mental Health Statistics

Data on the prevalence of mental disorders and alcohol and substance abuse disorders in women tend to differ widely, depending on the particular population studied and the methodology used to assess mental health. However, a 1988 report<sup>5</sup> on 1-month prevalence of mental disorders among individuals age 18 and older based on five epidemiologic

study sites revealed a substance abuse disorder prevalence of 4.5 per 100 women ages 18-24. This rate dropped off sharply after age 24, to 1.8 per 100 women for those ages 25-44 and 0.4 per 100 women among subjects ages 45-64. For males, the rate between ages 18-24 was 9.3 per 100 males. In strong contrast to trends noted in females, this rate remained high—at about 8 per 100—for males 25-44 years.

Among individuals of all ages over 18 years, the rate of affective disorders considered as a group was significantly higher in females (6.6 per 100) than in males (3.5 per 100). The rates increased from 5.3 per 100 females among the 18- to 24-year-old group to 8.2 per 100 among 25- to 44-year-old women. In women ages 45-64, there was a minor (nonsignificant) decrease, to 7.2 per 100.

Several of the affective disorders showed markedly higher prevalence in women. For example, the rate for a major depressive episode was 2.9 per 100 among all women age 18 and over versus 1.6 per 100 in men in the same age range. Also, considering all subjects, the anxiety disorders as a group were twice as common among females as among males (9.7 per 100 females versus 4.7 per 100 males).

## **Women's Physical Health—Overall**

Taken together, the statistics on morbidity in women (acute and chronic illness, physical and mental health) corroborate the general impression that although women live longer than men, they report more symptoms than men and may therefore experience poorer health for much of their longer life span. In addition to greater numbers of reported daily symptoms, a higher prevalence of many nonfatal chronic conditions, and a greater incidence of mental disorders among women, women's global assessments of their health status compare poorly with assessments made by men. In a 1989 survey, only 38.5 percent of women rated their health as "excellent," versus 43.0 percent of men.<sup>2</sup>

For a variety of reasons, women likewise visit physicians more often than men: in 1989, women had an average of 5.9 contacts with doctors, versus 4.8 for men.<sup>2</sup> More research is needed to determine

whether this higher level of utilization of health care among women is a cause or an effect: do women visit physicians more often because they are truly sicker than men, or do their more frequent visits elicit questions from physicians that lead to increased reporting of symptoms and conditions for women? New studies are required to validate and explain these higher levels of reported symptoms among females. However, some studies indicate that when women are working, they report fewer symptoms simply because they are too busy to make frequent visits to doctors' offices.

A key indicator of the health status of women is the delivery of healthy babies. Statistics on the percentage of infants that weigh less than 2,500 and 1,500 g at birth for selected U.S. racial and ethnic groups (Table 5) show that the United States is not doing very well according to this indicator and that there is considerable variation among the subgroups that make up the American population.

There is new evidence to support the theory that the weight and health of each newborn—and of subsequent generations of newborns—is strongly

**Table 5.**  
**Live Births 1988**

	<b>Percent Less Than</b>	
	<b>2,500g</b>	<b>1,500g</b>
Chinese	4.72	0.62
White	5.64	0.93
Native American	6.07	1.03
Hispanic	6.17	1.01
Japanese	6.17	0.84
Asian/Pacific Islander	6.25	0.85
Filipino	7.06	0.91
Black	12.97	2.78

Based on U.S. National Vital Statistics. From: *Health United States 1990*. US DHHS pub. no. (PHS) 91-1232.

influenced by the health of the mother and grandmother and that these intergenerational effects are probably mediated through intrauterine growth rate of each mother, most likely during the first and second trimester of pregnancy. According to this concept, the health of an infant depends on the health of the mother from her own conception to her baby's conception.

There is sufficient variation in pregnancy-related decisions among subgroups of women in the United States to make it likely that the background conception-to-conception profile of pregnant women collectively differs from one subgroup to another. This model has two important implications. First, no amount of current prenatal care is likely to eliminate all subgroup variations in infant birth weights and outcomes. Second, ideal future mothers are healthy women with good intrauterine and childhood growth records of their own.

## **Women's Health Behaviors**

Although the morbidity and mortality patterns observed among women have multiple causes that depend on an array of group and individual characteristics, researchers have nonetheless identified several areas in which women's choices of lifestyle probably have a profound impact on their health.

For example, because so many adolescent girls smoke, and because women as a group have been

***"We would underscore that there needs to be continuing research to change women's attitudes and behavior toward smoking. We are exceptionally concerned about the rate at which adolescent girls continue to engage in smoking cigarettes."***

*Jane Henney, Chair, Public Issues Committee, American Society of Clinical Oncology*

relatively resistant to efforts at smoking cessation, lung cancer rates are likely to reach epidemic proportions during the next 20-30 years. Other health consequences associated with smoking, such as low infant birth weight, heart disease, osteoporosis, and other cancers and respiratory diseases, will increase in parallel.

At present, more school-age girls than boys are regular smokers by the time they reach tenth grade (currently, however, fewer Black than white school girls smoke). Among adults, fewer confirmed female smokers than male smokers have quit smoking. It has therefore been predicted that in 2 or 3 years, there will be more female than male smokers in the U.S. population.

A second category of behavior that likely has multiple effects on women's health is type of diet. It has been hypothesized that a high proportion of cancers in postmenopausal women are associated with a high intake of dietary fat and that, if women reduced their total fat consumption by 50 percent, they could reduce their overall cancer incidence rates by as much as 30 percent (the comparable figure for men would be 17 percent). The same dietary restrictions could lower the incidence of heart disease by as much as one-third and, at the same time, diminish the risk of diabetes and high blood pressure.

Another important question related to diet is the extent to which adult obesity, independent of any unusual blood lipid pattern or metabolic disorder, is in itself a risk factor for coronary heart disease. This is of particular concern to Black women, who have higher rates of obesity than white women.

The third important area of behavior that bears upon the health of women is the use of contraceptives. Eighty percent of sexually active women have used oral contraceptives at one time or another. These medications came into wide usage before the long-term impact of their use on women's health could be carefully assessed. There has been ongoing concern that the long-term use of oral contraceptives may contribute to the risk of breast cancer. For all new contraceptives, there is

a need to develop methods to monitor effects so that these concerns do not recur.

## **Social and Cultural Factors**

Researchers are just beginning to explore the multitude of ways that the living environment and social forces influence a woman's physical health. The personal characteristics that define an individual's life—including gender, race/ethnicity, and socioeconomic status (SES)—appear to be associated with the various risk factors identified as direct or contributory causes of morbidity and mortality. In addition, some aspects of a woman's lifestyle—such as extent of education and choice of living quarters—affect not only the likelihood of developing some diseases, but also the likelihood of taking steps to avoid these and other diseases.

***“Yesterday, we heard some data on infant morbidity and mortality. The data on white women looked great. But let me tell you that if you look at data on Appalachian white women, they are just about the same as those on Black women in the nearby Cincinnati area.”***

*Evelyn Hess, Division Director,  
University of Cincinnati*

Perhaps the most notable example of these social and ethnic influences is the excessive number of health problems borne by those who are poor and/or who belong to racial and ethnic minorities. Another important example of the relevance of social influences comes from longitudinal research by McKinlay et al.<sup>6</sup> and indicates that among women in midlife, employment has a beneficial effect on how women perceive their health to the extent that changes in health that are expected

with aging and menopause are reversed or halted. These results suggest that work may alleviate stress arising from other nurturing roles and may therefore help to prevent morbidity in midlife women.

Researchers have not yet attained a full understanding of the interplay among the various social factors, nor of how these factors interact with inherited (genetic) factors in the causation (or prevention) of illness. In order to achieve this understanding, new strategies should be developed that combine findings from the many disciplines that are necessary components for research of this breadth.

## **Importance of Gender**

Traditional and newly emerging gender roles influence both the physical and mental health of women. From birth, women's lives differ in important ways from those of men. Women serve as caregivers to many people—including children, aging parents, and spouses. It is not yet known

***“We need to know if women defer consideration of their own health status while ensuring the well-being of others.”***

*Judy Auerbach, Government Liaison,  
Consortium of Social Science  
Associations*

whether the multiple burdens of providing care serve to make women stronger by fostering the development of coping mechanisms, or weaken them by inducing mental stress and physical exhaustion.

In addition to this traditional role, most women today also work outside the home in environments in which they may have to contend with new mental and physical stresses.

Research that fails to address the array of social factors affecting women's health—for example, job-related stress, low socioeconomic status, domestic violence, and substance abuse—would be incomplete. These issues need to be examined and

weighed in any comprehensive assessment of the current health status of women.

Researchers have found that in many instances, poverty and poor health are direct correlates. In one series of self-reports, for example, 65 percent of high-income individuals rated their health as excellent whereas only 32 percent of low-income individuals indicated that they considered their health to be excellent. Such data clearly support the notion that, to accurately assess the health status of women, the interplay of social factors must be examined.

## Diversity Among Women

While women as a group share many roles and behaviors, it is important to remember that women in fact compose a heterogeneous group of individuals who differ in significant ways. Their cultural and ethnic backgrounds are widely diverse. The following statistics regarding various health behaviors among subgroups of women demonstrates this heterogeneity.

There are important differences among groups of women in the extent that they use prenatal care, in the frequency of teenage pregnancy, and in their

*"The Hispanic population is the most rapidly growing ethnic group in the country and in the West the largest ethnic group. . . . The Hispanic groups, which include Mexican Americans, Puerto Ricans, Cuban Americans, and now Central Americans, are all quite different genetically and culturally, to some degree. What bothers me, I think, is the degree to which this group has been overlooked."*

Fernando S. Mendoza, Associate Professor, Department of Pediatrics, Stanford University and Director, Stanford Center for Chicano Research

rates of smoking. For example, 80 percent of white and Asian American women use prenatal care in pregnancy, but only 60 percent of Black, Hispanic, and Native American women use such care. Also, Black women have the highest percentage of adolescent pregnancies (23 percent), whereas Asian American women have the lowest (6 percent).

There may also be important variations within the traditional categories used to describe racial and ethnic groups. For example, the term Hispanics, as it is commonly used, includes Mexican Americans, Puerto Ricans, Central and South Americans, and Cubans within one group. However, the women from these countries may differ in important ways. For instance, Puerto Ricans in 1983 had a neonatal mortality rate that was 74 percent higher than that of Cuban Americans. The recognition of within-group heterogeneity is therefore highly significant for obtaining an accurate picture of the health status of all women in the United States.

## Influence of Personality Traits

Knowledge about personality traits is another consideration that is crucial to understanding how individuals adapt to stress, maintain psychological well-being, and make decisions about various health-related behaviors. Research on personality traits also can serve to dispel many of the myths about aging in women. For instance, stereotypic assumptions that older women become increasingly depressed, withdrawn, rigid, and irritable lack empirical foundation. Instead, studies have shown that individuals tend to preserve the same personality over time: in particular, the capacity to cope does not diminish with age.<sup>7</sup> What has not been investigated in women, however, is the extent to which particular personality traits may influence the development of various health problems.

## Combined Effects of Biological and Sociocultural Factors

There are significant differences in breast cancer morbidity and mortality in Black women versus white women. The difficulties involved in discerning which factors are in fact responsible for these differences and of establishing the relative importance of each factor illustrate the complexities

entailed in discerning the relative contributions of biological versus social influences in the development of disease.

Despite a lower incidence of breast cancer among Black women of all age groups, those who develop this disease experience a 10 percent decrease—at minimum—in survival times as compared with their white counterparts. The reasons for these differences are not known, but some factors that have been explored by researchers are SES, access to medical care, inherited (genetic) characteristics of women with breast cancer, tumor biology, type of treatment given, and compliance with therapy.<sup>8</sup>

Some evidence indicates that Black women who have breast cancer are not as likely as white women to receive the appropriate surgical or other kinds of treatment<sup>9</sup> and that care of Black women with breast cancer is of lower quality than that received by whites.<sup>10</sup> Other studies have reached different conclusions, judging that care of Black and white women with breast cancer was equivalent.<sup>11</sup> In one of these studies,<sup>9</sup> Black and white women with breast cancer who were matched for pretreatment characteristics were treated according to the same protocol. The results showed that Black patients had approximately 1.6 times the risk of death per unit of time compared with white patients. This indicates that the major determinants for survival were not related specifically to treatment. However, the investigators acknowledged that they were uncertain as to whether SES-related factors—not analyzed in the study—could have played a causal role in the observed difference in mortality.

A 1991 study addressed the association between family history of breast cancer and risk of breast cancer in Black women<sup>11</sup> and attempted to determine the genetic models that best describe familial patterns in this disease. As with white women, family history of breast cancer in a first-degree relative was found to be predictive of a particular woman's risk of developing breast cancer, and this relative risk was of the same order as for whites. But there was also a significant effect from both educational and SES level among the Black women studied that was difficult to integrate with the genetic data obtained. In addition,

the authors admitted that their conclusions of necessity were compromised by the fact that they had failed to gather data on the possible involvement of environmental risk factors in the development of breast cancer in the women studied.

As the limitations of these studies suggest, social, cultural, and behavioral variables must be considered—in addition to measures of physiological function—to achieve valid and clinically useful conclusions.

## ***Conclusion***

The findings mentioned here, supplemented in detail with the mortality and morbidity data included within the Life Span and Crosscutting Science working group reports that appear later in this document, underscore the significance of

*“For much too long, biomedical research has neglected women’s diseases and has focused attention on the illnesses that affect primarily men. I have no quarrel with what society felt was correct 25 years ago, but as we enter the 21st century, we must attend to the areas that in the past have been underfunded.”*

*Barbara Butler, Board Member, The Lupus Foundation of America, Inc.*

women's medical problems today. For many years, it has been presumed that, because women tend to live longer than men, they are in most important ways more physically robust and therefore enjoy greater health throughout their life span.

In fact, data on women's health suggest a picture of significantly greater morbidity and chronic debilitating illness in women than in men.

The research agenda discussed in the working group reports that follow provides a comprehensive

guide to shaping the Nation's biomedical research approach toward preventing and treating the diseases that increasingly place an undue burden on the health of women throughout their lives.

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# **ETHICAL AND LEGAL ISSUES: WOMEN AS RESEARCH SUBJECTS**

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# ETHICAL AND LEGAL ISSUES: WOMEN AS RESEARCH SUBJECTS

*Based on presentations by  
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**W**omen—especially pregnant women or women of childbearing age—are frequently underrepresented among the subject populations in scientific research. One explanation for this discrepancy derives from the “thalidomide disaster” of the early 1960s, when an antiemetic that was liberally prescribed for pregnant women in Europe and Australia was found to cause severe birth defects. Since that time, regulatory agencies, pharmaceutical companies, and researchers have been wary of involving women in research. However, in point of fact, there was an important distinction in the “thalidomide tragedy”: the women whose babies were harmed were not research subjects; they were patients.

During the years that followed the “thalidomide disaster,” both the Food and Drug Administration (FDA) and the pharmaceutical companies involved in developing new drugs added ever-increasing protections for people who were assumed to be particularly vulnerable study subjects. This group includes, but is not limited to, women and their fetuses or women who might be pregnant but unaware of the fact.

The perceived difficulty of ensuring protections for such potentially vulnerable female research subjects is one important reason why women have not served as research subjects in proportion to their representation in the population. For example, it has been assumed that any woman biologically capable of becoming pregnant might do so during the course of a clinical trial. Her developing fetus might then be susceptible to damage from the drug being tested, and major lawsuits and disastrous publicity could ensue. In fact, there are several means of conducting clinical trials using women of childbearing years with reasonable certainty of safety—for example, by recruiting women rendered sterile by tubal ligation or hysterectomy or women who are highly unlikely to become pregnant such as celibate and homosexual women.

However, there is another reason why the research questions that pertain specifically to women have had relatively low priority on the research agenda: there is a pervasive sense within the research community that many of the health issues of women are of secondary importance. These neglected research questions have concerned two types of diseases: those that occur solely in women, and those that occur in both women and men but have been studied chiefly in male subjects.

Much of this relative neglect of women's health issues has been influenced by the misperception that women are healthier than men; this assumption, in turn, relies upon selective use of misleading statistics that show the life span for women is, on average, longer than that for men and that women tend to be affected by only some major diseases or to be affected later in life. A prime example of male-oriented research on therapies for diseases that in fact afflict both men and women is the research on the prophylactic value of aspirin for coronary artery disease, initiated in 1981. These studies were conducted almost exclusively in men. Nonetheless, recommendations based on this research were promulgated for the general population, even though there may well be significant differences in the way in which women respond to aspirin therapy as compared with men.

### **Rationale for Ascertaining That Women Are Included in Research Trials**

In spite of the particular issues that can be raised as objections to including more women in research trials, it remains true that a categorical exclusion of young women from participation as study subjects in biomedical research is both unjust and unwise. Such a policy embraces the assumptions that either all women are potentially pregnant or that all drugs are potentially dangerous to fetuses. In fact, neither assumption is true. Moreover, a policy that excludes women from research but then exposes them to risks unknown because unstudied through the more haphazard route of medical practice, fails to protect the interests of women pertaining to obtaining the safest and most effective therapies.

Women may react differently to drugs than do men, and pregnant women may react differently than do nonpregnant women. Without adequate scientific evidence to guide them, physicians are compelled to improvise on dosages and choices of drugs for their female patients. Research has already identified some important gender-related differences in regard to the effects of drug therapies—such as how drugs are absorbed, the levels of therapeutic effect achieved, and the pathways by which drugs are eliminated from the body.

Acetaminophen, an antipyretic pain-relieving drug, for example, is eliminated far more rapidly in men than in women.<sup>1</sup> The drug is eliminated by women at about 60 percent of the rate typically seen in men. This might mean that a woman needs to take acetaminophen less often than a man because more of the drug remains in her body for a longer period of time. Different patterns of elimination might also place women at greater risk for side effects if, given identical drug dosages, they accumulate higher drug concentrations over time than do men.

Some researchers claim that the lack of research on women is a consequence of the fact that the changes that characterize women's reproductive cycles might affect test results by introducing significant variables that are not accounted for in study protocols. However, it is precisely because medications and other therapies may have different effects on women according to which point in the menstrual cycle they are administered that women of childbearing years should be included in research trials.

*"Approximately 80 percent of pharmaceutical products are taken by women. . . . What I would like to urge (is) to focus on how we can meet the practical issues of FDA-type studies. All of the hormones, as well as thyroid function tests, must be included in just about every study we do. These are the kinds of practical concerns we need to think about, along with the issue of incorporating women of reproductive age into clinical research."*

*Donnica L. Moore, M.D., Associate Director, Medical Education Center, Sandoz Pharmaceuticals*

For example, research has shown that the effects of some antidepressants change over the course of a woman's menstrual cycle.<sup>2</sup> As a consequence, there will be some points in the cycle when the proposed dosage of an antidepressant will be too high, and others when the dosage may be too low.

Other observers have noted additional factors that may result in discrepant reactions to therapies in women versus men. The fact that the ratio of fat to lean tissue is usually different in men than in women, for example, may influence how drugs are absorbed and eliminated. Also, the hormones that are commonly prescribed for women, such as birth control pills, may alter how women's bodies react to drugs and other therapies.<sup>1</sup>

### ***Efforts of the Office of Research on Women's Health***

At the time of its establishment in September 1990, one of the primary goals of the Office of Research on Women's Health (ORWH) was to develop special initiatives to acquire vitally needed research data on women by increasing the participation both of women as subjects in clinical trials research and of institutions and investigators in performing research related to the health of women. It was proposed that these initiatives could take the form of: regional or national meetings to alert investigators, institutions, and women themselves about the need for research on the health of women; materials to aid institutions and investigators in obtaining grant support in these areas; and forums on women's health.

An important precedent to this goal was the 1985 report of the Public Health Service Task Force on Women's Health Issues and its recommendations, including the recommendation that "biomedical and behavioral research should be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in, women in all age groups." To implement this recommendation, the National Institutes of Health (NIH) published a policy statement in 1986, *NIH Guide for Grants and Contracts*, which urged that applicants include women in clinical studies and in clinical trials especially.

Despite this recommendation, according to a General Accounting Office (GAO) report conducted in 1989, whether women were in fact being included in research populations was questionable. The GAO report focused particularly on compliance by grant applicants and NIH staff with the policy encouraging participation of women in clinical studies, and concluded that the 1986 policy was not being implemented uniformly across the NIH.

In response, the NIH staff determined that increased emphasis on research in women's health must become a top priority. One result was a new document: the revised *NIH Guide for Grants and Contracts*, published in 1990. The guide stipulates that NIH staff and peer advisory groups are to "ensure that applications/proposals for extramural support for clinical research studies involving human subjects include appropriate representation of women and minorities, unless a compelling justification is made for their exclusion or inadequate representation." Grants and awards that fail to comply will not be funded. In addition, a research grant application form that refers to this policy has been prepared; the form requests specific information about the inclusion of women and minorities in clinical studies.

To promote full implementation of this policy, all NIH professional staff in program and review areas attended training sessions held in September and October of 1990. The policy was also discussed at the fall meetings of all NIH initial peer review groups that review clinical applications and at the meetings of the various NIH advisory councils.

Also, in order to devise a rational means of addressing the number of real and complex issues that persist in spite of important NIH policy changes, the ORWH asked the Institute of Medicine (IOM) to prepare a report analyzing how to include women of childbearing age in clinical trials, among other issues and to develop recommendations for feasible means of resolving them.

## **Perceived Obstacles to Including Women in Research Trials**

The IOM study<sup>3</sup> had two major objectives: first, to determine whether it is feasible to develop guidelines as to whether a study to evaluate gender differences should be designed, and second, to identify ways of overcoming the major problems associated with the use of women in study populations.

The IOM report included a summary of the issues that arise most frequently as arguments against the use of women as biomedical study subjects:

- The cyclical hormonal changes that occur in women make them more difficult study subjects than men, in whom no such changes occur.
- Including women makes the study population less homogeneous.
- The cost of trials is significantly increased if the study population is enlarged sufficiently to allow the testing of gender-specific hypotheses or subgroup analyses.
- There are ethical reasons to avoid exposing existing or potential fetuses to harm.
- There are legal and financial consequences if a fetus or child is harmed as a result of the mother engaging in a trial.
- It is more difficult to enroll women into trials and to retain them for the specified duration of the trial.

## **Including Gender-Related Variables in Research Studies**

While it was not the purpose of the IOM report to arrive at specific strategies for overcoming these problems, the report did include recommendations to clarify the precise ramifications of these problems and did suggest general approaches for overcoming them. As a first step in this process, the report divided the list of issues cited above into two general categories of problems: the first group is related to the alleged increase in cost of studies if gender-related hypotheses were included,

while the second pertains to ethical and pragmatic barriers to enrolling women in research trials, especially the problem of how to provide adequate protection for damage to either the fetus or the fertility of the woman.

For example, since it would clearly be very expensive to require that every study include analyses of all possibly relevant demographic factors, such as race, gender, ethnicity, age, weight, hormonal status, and socioeconomic status (SES), the IOM determined that the development of guidelines for researchers would be useful for determining which biomedical studies should address gender-related issues. The report mentioned many possible sources for identifying areas in which gender differences might reasonably be expected to emerge

***"It's not a political statement to claim that women are unique. It's a biological and physiological fact: our efforts to address their health problems must reflect this basic reality."***

*Irma E. Goertzen, President,  
Magee-Womens Hospital*

as significant. These include epidemiologic evidence, data from basic studies, and findings from animal studies, as well as evidence from clinical studies (e.g., drug trials and postmarketing drug surveillance data).

The specific selection of gender-related variables for a particular research trial must depend to a great extent on the subject under study in that trial, but the IOM recommends that certain variables should be included in a broad array of trials: these include the hormonal status of women and variables related to the menstrual cycle, use of oral contraceptives, menopausal status, or use of estrogen replacement therapy.

To develop guidelines addressing which variables should be included in various research studies, some relatively straightforward approaches are

available, in the opinion of the working group. For example, if it is known that a particular drug is metabolized via pathways that are influenced by sex steroid hormones, that knowledge provides a clear indication that gender-specific hypotheses should be included in studies of the drug.

As a general consideration, the scope—and therefore the cost—of studies can be contained while still giving adequate consideration to possible gender-related differences by developing new research designs and statistical methodologies that can pave the way for smaller scale alternatives to the traditional large, expensive clinical trials. For example, in studies focusing on just one gender, only women may be used.

## *Women of Childbearing Potential*

While there are several problems that pertain to the use of women of childbearing potential, the IOM working group concluded that this need not mean that all women between the ages of 15 and 50 must be excluded from research studies. There are, the working group noted, many women between puberty and menopause for whom pregnancy is impossible—for example, among women rendered sterile by surgery, tubal ligation, or hysterectomy. Also, there are populations of women in whom pregnancy is highly unlikely, such as among celibate and homosexual women.

In addition, for most research studies it is possible to formulate relatively straightforward ethical guidelines concerning those women who have a greater likelihood of becoming pregnant during a drug trial. Some—and perhaps most—research protocols may not present any known or foreseeable risks to fetuses. For these protocols, there is no reason to exclude women, especially those who are not pregnant and do not plan to become pregnant.

In other instances, protocols may carry the possibility of minimal or even moderate risk to fetuses—as with some AIDS drug protocols, for example—but also great benefit to the woman, especially in the instance of a life-saving drug or cure. In this case, women should not be excluded automatically from trials, but instead be given

the opportunity to make their own assessment about the relative risk and benefits of participating after the risks and benefits—to themselves and to their fetuses—have been carefully explained.

There remains, however, the small but worrisome category of studies involving drugs that present high risk to fetuses but minimal or, at most, moderate benefit to women. Some argue that there are never any legitimate grounds for overriding a woman's autonomy and denying her the choice of whether to participate. In this view, valuing a fetus's welfare more highly than a woman's autonomy is objectionable in principle. However, most would agree that risks to fetuses cannot simply be dismissed as irrelevant. Nonetheless, it is difficult to determine what would constitute "serious" or "excessive" risks to the developing fetus.

At one extreme, the choices about including pregnant women or women of childbearing potential are relatively simple. Excluding a woman suffering from a life-threatening condition from access to a potentially life-saving drug on the grounds of harm to a fetus, which may or may not exist, seems not only harsh but unjust. Even if the woman were pregnant, or if her life were in danger, her fetus would be equally threatened. At the other extreme, to expose women and their fetuses to serious risks when there are alternative therapies is clearly unethical. In the vast majority of cases, however, women can be offered the same options as men, with full explanation of the risks and benefits to themselves as well as to their fetuses.

An essential element of all research in humans, the consent process is even more important in protocols involving women of reproductive potential—and men who might father children, although this is seldom considered. The investigator and the study's institutional review board must ensure that the protocols and attendant risks and benefits, as well as alternatives to the research, are fully discussed in language and terms that the potential subject understands. Where literacy is a problem, visual aids can be used. Equally important, researchers must ensure that the clarity of the explanation of risks versus benefits is not compromised by ethnic or cultural barriers: all materials

intended for potential study subjects must be culturally sensitive.

While the issue of possible liability is often cited as one rationale for excluding women of childbearing age from trials, the IOM working group noted that very few liability cases arising from women's participation in clinical trials have actually been brought to court, and those that have been were usually unsuccessful. Conversely, there have been large settlements rendered against pharmaceutical companies in cases where women were harmed by drugs that had been tested solely in men.

## ***Recruitment and Retention of Women in Trials***

***"A promising opportunity for research rests in the area of recruiting women of diverse ages and circumstances into clinical research trials, traditionally a major challenge for investigators. Innovative models for community-based research have recently been reported."***

*Beverly Baker, Executive Director,  
National Women's Health Network*

Some researchers believe that it is difficult to recruit and retain women in clinical trials. This belief, however, is based largely upon anecdotal information. Nonetheless, there are some potential problems that may make participation in extended trials onerous for women. Many of these problems are simple consequences of the multiple and time-consuming roles that women play in society today; they often have special needs with regard to child care, transportation, and other family responsibilities.

Recruitment efforts directed at women, therefore, need to account for women's multiple roles, including the fact that women are often employed in

low-status or marginal jobs that offer few opportunities for flexibility in the required hours of work. Researchers must also bear in mind that for many women, meeting their own health care needs may not be their highest priority; enrolling in a research study, with its possible demands on both time and lifestyle, may seem even less important.

Researchers have found that utilizing the mass media is an effective method for recruiting subjects into trials. However, this approach principally attracts white middle-class male subjects. Therefore, persuading women to enroll in clinical trials—especially low SES and minority women—may require some special effort at overcoming what has become, in many areas, a general mistrust of the medical establishment. These efforts frequently involve forming new kinds of relationships between clinical researchers and the surrounding community so that members of the community share in the decision-making process that guides research studies.

In particular, researchers may benefit from identifying the gatekeepers within the community who will provide access to community members and serve as a crucial link between the community and the research center. These gatekeepers need to be involved from the earliest planning stages—optimally, from the time that the studies are designed—so that they can provide guidance on issues such as literacy and informed consent for potential study participants. These gatekeepers can also help in identifying women who, with appropriate training, can serve as members of the research team.

Perhaps most important, researchers must continually stress the reciprocal nature of research. They need to reinforce the concept that, in addition to the obvious benefits they are providing to the researchers, study participants are benefiting themselves and their communities through gains in the efficacy of health care achievable through the successful implementation of research protocols.

Retaining female study subjects may also require innovative policies aimed at meeting the special needs of women. For example, women may require reimbursement for child care expenses, transpor-

tation to the research clinic, or more flexible hours of operation at the clinic because of the extreme demands placed on the time of many women.

It is important to bear in mind that the overriding goal of all the efforts aimed at enrolling and retaining women as study subjects is not to compel women to become research subjects, either for their own good or for the good of society but instead to make more equitable the selection of subjects who will undertake the risks and share in the benefits of research.

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# WOMEN IN BIOMEDICAL RESEARCH

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# WOMEN IN BIOMEDICAL RESEARCH

*Based on a presentation made by  
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**B**y the year 2000, one-third of all the people entering the work force in this country at any level will be women. By the same year, demographers predict a significant shortfall in the number of biomedical and behavioral scientists, due in part to the fact that fewer white males are choosing science as a career.

In the past 2 years, these predictions have prompted considerable concern at the national level about the underrepresentation of women and minorities in science and engineering. Because it is members of these groups who can provide a solution to the anticipated shortage in the science professions, we now have a unique window of opportunity for promoting greater participation of women and minorities in biomedical research.

In response to the anticipated shortage of scientists, many research institutions have commissioned studies on how to improve both recruitment and retention of female students and faculty in science and engineering. Programs also are being created by the Federal Government and in private and philanthropic organizations to encourage the inclusion in science programs of women and minorities who

have varying levels of education. There are important questions, however, that remain unanswered about what realistically can be expected from such efforts.

## ***Data on Participation of Women in Scientific Careers***

To determine the outcome of current recruitment activities, it is necessary to understand what has prevented women in the past from participating more fully in scientific fields. From one perspective, women appear to have made major gains in academic achievement. Over the past 22 years (1966-1988), the percentage of women receiving degrees in science and engineering has increased dramatically (Table 1). For example, in 1966, 23 percent of the bachelor's degrees in science and engineering were awarded to women; by 1988, the number had nearly doubled, to 40 percent.

For Ph.D. degrees, the numbers have risen from 9 percent in 1966 to 27 percent in 1988, a threefold increase. However, there remains a strong contrast between the percentage of Ph.D. recipients who are women in the sciences as opposed to the humanities:

**Table 1.**  
**Academic Degrees Among Women,  
 Science and Engineering, 1966-1988**

Academic Degree	% Awarded to Women	
	1966	1988
Bachelor's, science and engineering	23%	40%
Ph.D., science and engineering	9%	27%

48 percent of all the Ph.D.s in the humanities are currently being awarded to women. Also, increases have not been steady over the 22 years: most gains were achieved during the 1970s, and very little progress has occurred since 1982. In fact, there may be a leveling off at this point in terms of women's participation in science and engineering.

Furthermore, these percentages represent averages from the many highly disparate disciplines that fall under the overall umbrella of science and engineering. And the differences from one field to another are great: in psychology, for example, more than half of the new Ph.D.s are women, whereas in engineering, only 7 percent are women.

Sizeable gains for women also have occurred at the postgraduate level, although only anecdotal evidence exists with regard to the career choices of women who received higher degrees in either science or engineering. Additional comprehensive studies are needed to find out what happens to women after they receive their Ph.D.s.

But from another perspective, there is considerable evidence about the enormous problems—and resulting discontent—experienced by women in the sciences. An article that appeared in *Science* magazine in 1991, "Still a 'Chilly Climate' for Women?",<sup>1</sup> details the course of attrition in the representation of women in the discipline of physics.

As a group, women represent 51 percent of the population (Table 2). Among high school students studying physics, 35 percent are women, but in universities, only 22 percent of students who take an introductory course on physics are women; only 16 percent who receive their bachelor's degree in physics are women; and only 10 percent of all Ph.D.s in physics are women. Seven percent of assistant professors of physics are women, and only 3 percent of those who eventually attain tenured faculty positions within the physics departments of the major research universities are women. At each step in the academic career ladder, significant numbers of women are dropping out, perhaps concluding as they do so that the field of physics is not one in which they can successfully persevere.

### ***Disparities in Science Education Between Females and Males***

Differences between the two genders with regard to science can be detected as early as 9 years of age, and girls report fewer science-related experiences, such as looking through a telescope or measuring how long a process takes by using a stopwatch.<sup>2</sup> By the age of 13, girls are less likely than boys to read science articles in books, watch science shows on television, or have science hobbies. Until the tenth grade, this discrepancy in the experiences of boys versus girls does not result in observable differences in the number of science and mathematics courses taken by boys and girls, but it does translate into differences in attitudes about careers in science.

The relative decline in women's participation in science observable by tenth grade is not reversed at any point thereafter. In college, even though the number of freshmen with declared majors is three times the number who actually will graduate with a degree in science and engineering, the percentage decline is greater for women than for men, with one notable exception: women's colleges lose far fewer of their science undergraduates to other fields.

In graduate school, the decline persists, even in fields such as biology, where women have been

**Table 2.**  
**Attrition of Women in the Discipline of Physics**

Women Represented in:	% of Group
Total U.S. population	51
High school students studying physics	35
Students taking introductory course in physics at college	22
Recipients of bachelor's degrees in physics	16
Recipients of Ph.D. degrees in physics	10
Assistant professors of physics	7
Tenured professors of physics at major research universities	3

represented fairly well. Although 50 percent of bachelor's degrees are awarded to women, only 40 percent of graduate school enrollment comprises women. This decrease in graduate school enrollment is especially pronounced in mathematics and computer science. Women are awarded almost 50 percent of the undergraduate degrees in mathematics; however, only 25 percent of such graduates actually pursue advanced degrees. This diminution continues at a larger attrition rate within graduate school, resulting in an even smaller percentage of women with Ph.D. degrees.

These data indicate the need to understand why so many women decide that they cannot continue on the academic path that leads to a career in science or engineering and suggest that intervention strategies be devised for nearly every step of the educational ladder to promote the retention of women in science and engineering programs.

## Changing the Male-Dominated Culture of Science

One reason for the low levels of participation of women in science relates to the culture of science as it is practiced in this country. To a considerable extent, society—and particularly educators—have failed to associate women with careers in science. Many times, the achievements of women, when they do persist in science careers, are discounted. The fact that women consistently receive negative messages about the feasibility of pursuing a rewarding career in science is the most probable explanation for their underrepresentation within the science and engineering professions.

A solution to this problem is to recruit more women into science. When the number of women within a discipline reaches a critical mass, barriers begin to slip away. Many programs attempting to effect changes in fields like physics where women are very much underrepresented focus their interventions early in the educational process. However, it may be more effective—at least in the short term—to focus at the top, at the senior faculty level. Senior faculty women are able to participate in decision-making—which can include important decisions on hiring and promotion. These women also serve as key role models for young students and junior faculty. By acting as mentors and role models, they can interpret

***"More women researchers will be needed. Programs should be designed to identify and nurture the female researchers among high school and college students. Mentors should be found for women medical students, residents, and researchers, and technical assistance should be provided to overcome past inequalities."***

Roselyn Payne Epps, National President, American Medical Women's Association, Inc.

not just the particulars of a given science to their female students but also the scientific culture.

This potential solution is tempered by the reality that there simply are not enough women in fields of science. And focusing on the hiring and retention of senior faculty women is clearly not a universally applicable solution at present. But this strategy can be effective at the schools that are prepared to effect change rapidly and take a leadership role.

### ***Constraints for Women in Science***

The tremendous demands on time required to obtain the requisite training for a science career and then to pursue that career successfully affect dramatically the prospects for increasing women's participation in science careers.

When a woman entered a science career in the 1940s and 1950s, she was expected to renounce any intention of having a family. To a great extent, this expectation persists to this day. Women have paid an extremely high—and unequal—price for the successes they have achieved in science in the past 20 years. While some women willingly forgo a traditional family life, the majority do not.

The problem of reconciling the demands of a scientific career with a traditional lifestyle is exacerbated by the established tenure system at most academic institutions in this country. A woman is usually 30 years old before she assumes a professorship at a university, and her tenure decision normally occurs about 5 years later. Thus, her critical years for scientific research, when she is establishing her scientific reputation, coincide with her peak reproductive years. Many women forgo childbirth until they attain tenure but then must decide whether it is too late to plan a family.

Institutions are beginning to experiment with creative solutions to the problem of women having to choose between the attainment of tenure and a family. Some institutions have initiated programs that allow women 1 or more extra years before the tenure decision so that they can accumulate more research publications in compensation for the

time lost in childbearing. Others have adopted a gender-blind policy that allows fathers to adopt this option as well.

It has been suggested that an approach to leveling the academic playing field would be to abolish tenure altogether and instead, institute rolling appointments that are reviewed quarterly. This action could be beneficial for women because it would allow them to choose for themselves the best way to allot their time between research and family without having to give primary concern to a career clock that is inexorably counting down to a make-or-break tenure decision.

The ultimate solution to increasing the participation of women in science, however, must resolve the basic conflict between family and work that confronts women in nearly every profession. Perhaps the best means of accomplishing this objective would be to create a workplace in which there is a healthier balance between family and work. While science as a profession can never guarantee regular hours, it is flawed thinking to equate the quantity of time spent in a laboratory with the quality of the work produced there.

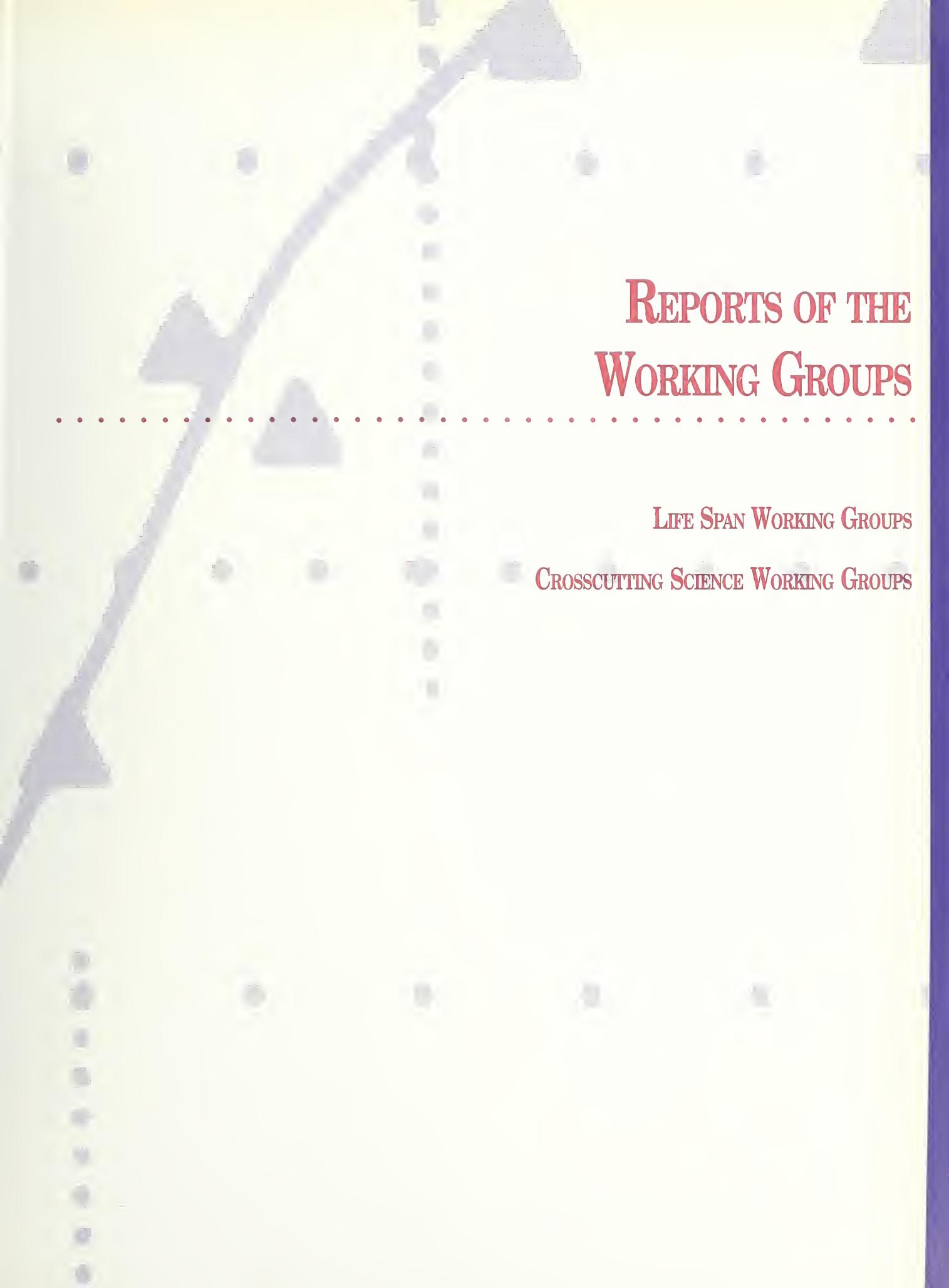
It would indeed be unfortunate if the obstacles that currently keep women from careers in science were to remain so formidable that women are not able to enter biomedical research in greater numbers in the coming years. It is likewise unacceptable that women in science will never reach parity with men or that they will continue to pay an unequal price for their success. There are few other professions in which the excitement that motivates a person to enter the field in the first place is so amply sustained over so many years.

In addition, recruiting more women into science and engineering will convey important benefits on the Nation. For instance, the women's health agenda detailed in this report would be enormously enhanced, and gender disparities in medical treatment and research could be significantly reduced by increasing the number of women in leadership positions in teaching, research, and the practice of medicine.

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# REPORTS OF THE WORKING GROUPS

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LIFE SPAN WORKING GROUPS

CROSSCUTTING SCIENCE WORKING GROUPS

Note: Each working group report underwent review and revisions with participation and final approval by the cochairs of the respective working group.

# BIRTH TO YOUNG ADULTHOOD

*Cochairs:*  
*Alain Joffe, M.D.*  
*Roselyn Payne Epps, M.D.*

**I**n no other portion of a woman's life span do such dramatic changes occur as during the two decades between birth and young adulthood. Beyond the first year of life, the prevalence, incidence, and costs of mortality and morbidity among girls and young women are related less to disability and disease than to injuries, environmental exposures/hazards, and risk-taking. The key issues thus pertain to recognizing the key determinants of wellness in girls and young women and learning how to sustain their good health. These efforts must be conducted across economic and cultural group borders and within the context of a society that has not always taken the health of girls and women seriously.

From early childhood to at least early adolescence, the health of a girl must be understood in part as an interdependent relationship with the primary caregiver, usually the mother or another woman. For example, the caregiver acts as an interpreter of symptoms and wellness and makes decisions about when to visit a physician or hospital. It is important, therefore, that efforts to improve the health of girls seek to enlist the cooperation and

support of all involved individuals, because caregivers are the individuals who socialize girls regarding health-promoting versus health-damaging behavior.

The potential to achieve significant increases in the life span and quality of life of women is greatest at these young ages. Because many precursors of chronic diseases and disability occur in utero, and in infancy, childhood, and adolescence, research leading to strategies for sustaining the health of girls and young women is exceptionally cost-effective.

## ***Major Themes***

Certain major themes emerged from the working group deliberations. While each may be particularly relevant to one age rather than another, the following provides an overview of the issues discussed in greater detail within the age-specific sections of this working group's report.

We need a better understanding of the biologic differences between males and females across all age groups. That is, we need to know not only how males and females are biologically different but,

in addition, how these biologic differences exert their effects. Research in this area should consider such issues as the survival advantage observed for females, as well as the diseases that are more common in women (e.g., congenital dislocation of the hips, scoliosis, and autoimmune disorders).

***“...[A] gap in the research on the normal growth and development patterns of women is evident.”***

*Barbara Redman, Department of Congressional and Agency Relations, American Nurses' Association*

At the same time, the patterns of normal development among females across all ages must be delineated, taking into account the fact that girls grow to maturity in a society that is not gender neutral. Emphasis must be placed on the variability among females, with the understanding that “normal development” is affected by racial, cultural, and socioeconomic factors. The experience of growing up female is likely to differ considerably according to the family and community within which a woman matures.

Many of the diseases that cause significant morbidity and mortality among adult women have their onset in childhood and adolescence. Choices about lifestyle made during these years can have a profound impact on later susceptibility or resistance to disease; however, the range of choices may be limited by economic or cultural conditions. Therefore, it is necessary to know how girls and young women make choices about behaviors that are health-promoting (sensible eating, exercising, postponing sexual intercourse, using effective contraception, practicing safe sex, or practicing breast self-examination beginning in adolescence) and health-risking (using alcohol, tobacco, and other harmful substances; driving while intoxicated; purging food, or severely restricting caloric intake).

By the time girls enter adolescence, gender differences are clearly established concerning mental health, as measured by indicators such as rates of depression and suicide gestures. Because mental health issues are very important for this age group, more knowledge is needed regarding the biologic underpinnings of depression, the relationship between poor academic performance and depression, and the indicators of depression in childhood. Similarly, a clearer understanding must likewise be obtained of the interrelationship between society's emphasis on women's physical attractiveness, girls' own concerns about their bodies, and the development of eating disorders, obesity, depression, and suicide.

Injuries are the leading cause of morbidity and mortality among girls and young women. We need to know much more about the epidemiology of injuries among these groups. Many children and adolescents are raised in families and communities where violence is a daily occurrence. Many girls die from, or are injured by, acts of physical and sexual violence. How does being raised in such an environment affect the psychological development of girls? What are the biologic and psychologic effects on girls of being sexually and physically abused? What effect does rape trauma syndrome have on girls?

It has been estimated that some 10 percent of children and youths have a chronic disease or physical disability. Some of these conditions (autoimmune disorders such as lupus erythematosus and juvenile rheumatoid arthritis, scoliosis, and thyroid disorders) are more prevalent among females and/or have their onset or worsen during puberty. The biologic basis for these statistics should be explored, as should the effect of having a chronic disease on an individual's subsequent physiologic and psychologic development.

Finally, a general issue pertaining to women's health is how women adapt to pregnancy and the parenting role. More knowledge is needed in this area if we are to understand the impact of very early pregnancy and parenting on young women's subsequent development to adulthood.

## **Key Issues/Research Recommendations**

### **Prenatal Period to Infancy**

This age group is reviewed from two perspectives: research pertaining to the health of the female fetus and newborn and research addressing the impact of pregnancy, delivery, and childrearing on the health of the mother.

#### **Health of the Female Fetus and Newborn**

- More research is needed on the biological basis of sex differences, such as sexual differentiation in utero, differences in the survival rates of females beginning in utero, growth rates, and neurological development. Special consideration should be given to racial and ethnic variations in survival rates. Further, the biologic basis for the greater prevalence of certain birth defects among females (e.g., congenital hip dislocations) should be explored.
- Research should focus on the pharmacology of maternal and fetal interaction during this age period. Examples include studying differing responses of male and female fetuses to maternal use of diethylstilbestrol (DES) or glucocorticoids.

#### **Health of the Mother**

In addressing the health of women during the perinatal period, differences in ethnic, racial, and socioeconomic factors need to be considered. For example, health practices and the incidence of low-birth-weight infants vary considerably among female Hispanics of Puerto Rican, Cuban, Mexican-American, and Central American origin.

Little is known about the best treatments for pre-existing diseases during pregnancy and the impact of treatments (including drugs) on the fetus. Such research is hampered by ethical, clinical, and legal concerns for the fetus. Although these concerns are valid, failure to resolve them satisfactorily may ultimately be detrimental to the fetus, the mother, or both. Ongoing studies on the prevention and treatment of chemical dependency and AIDS should focus on the special implications of these conditions for women who are considering becoming pregnant.

- More research is required to develop new non-invasive diagnostic techniques for monitoring the status of the fetus and identifying problems.
- It is necessary to understand better the manifestations and effects of depression and stress, their profiles throughout gestation and the postpartum period, and appropriate methods for early diagnosis and management.
- Research is needed on the impact of breast-feeding on the mother (e.g., changes in dietary intake and the impact of medication and other substances), and the relationship between breast-feeding and decreases in breast cancer risk and bone density in later life.
- More research is needed to address the effect of caring for low-birth-weight infants, children with birth defects, and children with disabilities on the physical and mental health of women.
- Additional research is required to determine the consequences of pregnancy for women's well-being.

### **Early and Middle Childhood**

#### **Normal Development**

When the normative levels of functioning during childhood have been determined, the changes brought about by puberty can be better understood.

- Research into the normal physical and biological development of female children is required. Investigations targeting psychological and sexual development, including gender identity and sexual orientation, are needed. Basic studies are necessary to determine the factors that may predispose girls of diverse ethnic groups to specific diseases, behaviors, and levels of physical strength.

#### **Obesity**

Obesity, a prevalent problem in this age group, may be attributable to genetic influences, poor nutritional practices, family or cultural practices, and physical inactivity.

- Further studies are needed on the epidemiology and etiology of obesity across ethnic groups and on the long-term physical and social effects of obesity.

### ***Injuries/Risk-Taking***

Injuries are the leading cause of mortality and disability in childhood. Data on injury rates clearly indicate an excess of injuries among males, as compared with females, at each age during childhood. Perhaps because boys are more likely to incur injuries, fewer studies have examined the biological, environmental, and cognitive factors that place girls at risk for injuries.

- Studies are needed to examine the behavioral and environmental determinants of injuries among girls, the types of injuries girls experience, and the social and economic costs of injuries for females.
- Research is needed to examine the co-occurrence of other risk behaviors—such as tobacco, alcohol, and drug use—with injuries among girls.
- Research should identify the individual social and environmental characteristics associated with girls at persistent risk for injury and how they differ from those who experience very few or no injuries during a given time period.

### ***Chronic Illness***

Children who have a chronic illness are at increased risk of secondary psychosocial and behavioral problems. Their mothers may suffer from the extraordinary stress resulting from the commitment required of the primary care-giver. Such biological vicissitudes offer opportunities for preventive interventions.

### ***Family Issues***

Studies on divorce and remarriage have found significant gender differences in the ways children and adolescents react to changes in marital situations. Although findings are conflicting, the literature suggests that in late childhood and early adolescence, daughters have negative psychological reactions when their mothers remarry and that these reactions are more intense than those of sons.

Another area for research on the psychosocial development of females is the influence of verbal, physical, and sexual violence in families.

- Research is needed to examine the long-term mental health consequences of marital transitions on girls. Of all children under 18 years of age, 25 to 30 percent experience a family breakup due to marital separation or divorce. Since the patterns of marital status and disruption vary across ethnic groups, such studies should investigate ethnic differences and similarities in the long-term consequences of marital transitions.
- Studies should investigate whether the negative consequences noted for girls in this age range are applicable to girls from different racial, ethnic, and socioeconomic groups, since many studies of divorced families have used white lower- to middle-class subjects.
- Research is needed on the connection between family violence during a girl's childhood and subsequent risk-taking behaviors in adolescence, such as early unprotected sexual intercourse, delinquency, tobacco, alcohol, and other drug use.
- Epidemiologic studies are needed on the prevalence of sexual and physical abuse against females.
- Research should be conducted to examine ethnic and cultural variations in perceptions of women and how these differing views may protect or place some girls at greater risk for abuse.

### ***Aspirations and Self-Esteem***

- Studies are needed on the development of self-esteem in girls, its ebb and flow during childhood, and its possible connection with decreases in risk-taking behaviors.
- Research should investigate how aspirations and perceived educational and occupational opportunities for girls during childhood enhance their choice of healthy lifestyles during childhood and adolescence. Of particular importance is the relationship of body image to self-esteem in girls.

## **Health Promotion**

***"Too little attention and resources have been placed on understanding the behavioral and social dimensions of health—why people do or do not engage in healthy behaviors."***

*Judy Auerbach, Government Liaison, Consortium of Social Science Associations*

The antecedents of healthy and unhealthy behaviors begin in early and middle childhood. The range of options among these behaviors, however, may be limited by social, cultural, and economic factors.

- Research is needed on the contributions of protective factors—for example, good nutrition, exercise, high self-esteem, and adequate sleep—to the health status of girls.
- Studies should be pursued that will develop and evaluate preventive interventions addressing smoking, substance abuse, poor nutrition, risk-taking behaviors, violence, physical inactivity, poor oral health care, the development of inadequate social skills, unintended pregnancies (including studies on safe and effective contraceptives), and sexually transmitted diseases.

## **Mental Health and Depression**

Symptoms of mental health disorders that occur frequently in females may be more subtle than those in males, and hence go undiagnosed in their early stages.

- Because rates of major depression increase in girls after puberty (and remain higher for females than males throughout life), early predictors of onset of depression need to be determined.
- The biological and sociocultural factors in childhood that put females at greater risk for depression later in life need to be understood.

## **Adolescence to Young Adulthood**

### ***Developmental Issues***

The normal pubertal, cognitive, and psychosocial development of adolescent females needs to be identified within a contextual framework. Particular attention must be paid to the physiological basis for variations in the onset of puberty and its progression, and the effects this variation can have on the self-image and behavior of adolescents. Issues of sexuality for this age group also need to be explored. Many of the themes related to sexuality that have been stressed in the past may be outdated and/or culturally inappropriate for contemporary adolescents. In addition, study samples of this age group should reflect ethnic minorities and socioeconomic diversity. Also, basic biologic research should proceed concurrently with behavioral research—for example, by investigating the interactions of both steroid and protein hormones and growth factors with behavior.

When the parameters that define normal for females have been described more completely, knowledge about the relationship between pubertal development and other health issues, such as chronic illness and metabolism of medications, should follow.

- Parameters of optimal physical functioning—that is, exercise capacity—should be outlined to gain a better understanding of young women's full biologic potential. Optimal limits may vary by ethnicity, body habitus, pubertal staging, or other parameters.
- Studies should investigate the effects of pregnancy, childbirth, rearing of children, and abortions on subsequent development, since many adolescents have these experiences.

### ***Wellness and Risk-Taking Behaviors***

Directing more attention to the etiology, diagnosis, classification, treatment, and long-term outcome of eating disorders among adolescent females can shed light on healthful behaviors for young females.

Adolescent females are competing in strenuous athletics in increasing numbers; such participation can lead to changes in body composition and

to abnormalities in menstrual function, including amenorrhea and low estrogen levels. These changes, in turn, can lead to loss of bone mineral density.

***"We need a better understanding of how to increase peak bone mass in young adulthood so that there will be a greater bone reserve to offset bone loss later in life. We need a better understanding of how estrogen and other regulatory hormones affect the skeleton in order to develop new methods of treatment."***

Sandra C. Raymond, Executive Director, National Osteoporosis Foundation

- Studies should look into strategies for teaching adolescent females responsible health behaviors that encourage beneficial decision-making.
- Research is needed to understand the interaction among biological, psychological, and social factors that lead to harmful behaviors such as early and unprotected sexual activity, use of harmful substances (especially cigarette smoking and use of alcohol), and risky behaviors such as reckless driving.
- Research is needed to find out whether there are any developmental factors that play a role in whether women will adopt a proper diet. There is evidence that cancer risks can be reduced twice as much in women as in men by adherence to a low-fat diet.
- Prospective longitudinal studies are needed on sexually active young women to determine the short- and long-term consequences of sexually transmitted diseases, including infection with human immunodeficiency virus, human papilloma virus, and chlamydia, as well as pelvic inflammatory disease.

- Investigations should examine whether multiple sources of stress affect risk-taking behaviors and, in contrast, which factors render girls more resilient to stress.
- Investigations should analyze the impact of behavioral patterns on women's health and how individuals with these disturbances respond to disease.
- Research is needed on the relationships among exercise, body composition, nutrient intake, menstrual function, and osteoporosis in young women.

### **Mental Health**

Depression in postpubertal girls is a significant problem. Symptoms of mental health disorders in females may be more subtle than those in males, and hence go undiagnosed in their early stages.

- Because rates of depression for girls rise after adolescence, an emphasis on the biological and psychosocial mechanisms that make women more vulnerable should be studied, and the importance of choosing appropriate treatment approaches should be emphasized.
- Subtypes of depressive illness that have higher rates in women, such as rapid cycling disorder, also should be studied.
- Indicators of mental health risk in preadolescent and early-adolescent girls should be identified. Such indicators may include poor academic performance, a measure already linked to other adverse health outcomes.
- Research is needed to clarify the patterns and mechanisms of substance use by adolescent females—specifically, nonuse, experimentation, heavy use, and addiction. The influence of gender roles and relationships with male partners should receive special attention in these studies.
- Studies should explore the link between high-risk behavior patterns—such as addictive behaviors and eating disorders—to neurobiologic abnormalities.

- Research is needed on the factors that either protect girls from, or increase their risk for, suicide gestures. These should include studies examining the nature of the linkages among suicide and drug use, depression, and eating disorders.

### **Injury**

- Further study needs to be conducted on the risk-related behaviors that render young women more vulnerable to intentional and unintentional injuries. According to recent data, the impact of sexual abuse and molestation on subsequent psychosocial development (both sexual and nonsexual) has implications for significant numbers of young women.

### **Special Issues**

To define priorities for research on women's health from birth to young adulthood, several issues concerning methodology are worth noting.

- It is crucial that valid and reliable measures of behavior be developed for different ethnic and age groups. Such instruments can facilitate understanding of certain topics in behavioral research.

***“Health-promoting behaviors must be examined throughout a woman’s life, not at one or two specific points.”***

Beverly Baker, Executive Director,  
National Women's Health Network

- Studies also should determine reliable and valid indicators, measures, and screening techniques for assessing the general health status of girls and young women at all stages of development.

The distinction between behavior and biology is artificial. All future research efforts should aim at merging these two areas whenever it is appropriate. Because most studies devoted to women's health issues will require input from specialists

such as clinicians, psychologists, behavioral scientists, and methodologists, future research on women's health must be interdisciplinary.

- Longitudinal research is needed to follow the course of females through their entire life cycle. Studies of young girls should follow a cohort for several years or decades. These goals may be more easily achieved when components of the Alcohol, Drug Abuse, and Mental Health Administration are under the NIH umbrella.

The development, implementation, and evaluation of multimodal treatments that involve biological and psychological therapies may be necessary for certain diseases. For example, some patients with depression, while requiring psychotropic medications, may also need psychotherapy to effect a resolution of symptoms. Sorting out the individual, as well as combined, effects of multimodal treatments will require new methodologies.

- Studies are needed that focus on within-gender differences, as well as male-female differences.
- Research should define normal health for girls from birth through young adulthood.

Acquiring access to diverse research populations of females is crucial to establishing the range of normal and abnormal conditions in women. It is important that research involving special populations not begin with a premise of pathology but instead consider some of their particular advantages, for example, the decreased incidence of low-birth-weight infants and neonatal mortality in the Hispanic population and the lower incidence of osteoporosis in Black females. Studies must be ethically and economically feasible, and they should utilize incentives and creativity to motivate participants. The special needs of women who are solely responsible for the care of their children must be taken into account. Protocols involving the study of sensitive behaviors among adolescents (e.g., sexual activity) must address the difficult issue of an adolescent's capacity to consent and participate without the knowledge of her parents. Also, interdisciplinary involvement is important to ensure broad dissemination of research findings.



## **YOUNG ADULTHOOD TO PERIMENOPAUSAL YEARS**

*Cochairs:*  
*Gloria E. Sarto, M.D., Ph.D.*  
*Judith N. Wasserheit, M.D.*

**T**he importance of a health problem is often measured in terms of resultant mortality due to the profound emotional impact of death as well as the relative ease of counting deaths. However, particularly for American women in the 15- to 45-year age range, morbidity is an equally valid criterion for prioritization of health research.

Overall, mortality rates in the United States among 15- to 45-year-old women are relatively low (79 per 100,000 in 1988). Data from the National Center for Health Statistics (NCHS) indicate that, in 1988, the leading causes of death in this age group included malignancies, injuries (unintentional, suicides, and homicides), cardiovascular diseases, AIDS, and liver disease (Table 1). Cause-specific death rates for women show that mortality due to cardiovascular diseases, homicides, and AIDS is much higher among Blacks than among whites (Table 2). With the exception of cancer mortality, rates are uniformly lower for women than for men (Table 2).

The years from young adulthood to menopause should, in fact, be a woman's most productive years, not only as a member of her society and

her family, but also in terms of personal growth. Yet, because these are also the reproductive years, optimal productivity and personal development depend in large measure upon a woman's ability to live free of morbidity in terms of sexual function, fertility regulation, pregnancy, and delivery. Critically important health issues in this constellation are prevention and control of sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV) infection.

In addition to the prominent roles of sexual function and reproduction in the lives of women from young adulthood to menopause, several other health issues frequently have adverse effects on women in this age range. Psychosocial morbidity (e.g., depression, substance abuse, and sexual and physical abuse) may disproportionately compromise the health of women during this period, perhaps in part due to gender-related inequities in social and financial resources. Injuries, malignancies, and cardiovascular diseases, often thought of as health problems that occur primarily in men or in older women, are also major causes of disability and mortality in adult women prior to menopause.

Table 1.  
**Deaths Among U.S. Females 15 to 44 Years, All Races, by Disease Group  
 1988**

<b>Group</b>	<b>Cause of Death</b>	<b>Number of Deaths</b>	<b>Percent</b>
2	Certain other intestinal infections	4	0.0
3	Tuberculosis	111	0.2
4	Tuberculosis of respiratory system	(65)	
5	Other tuberculosis	(46)	
8	Meningococcal infection	30	0.1
9	Septicemia	404	0.9
11	Measles	1	0.0
12	Viral hepatitis	92	0.2
13	Syphilis	3	0.0
14	All other infectious and parasitic diseases	1,819	3.9
15	Malignant neoplasms, including neoplasms	12,102	26.2
16	Malignant neoplasms of lip, oral cavity	(112)	
17	Malignant neoplasms of digestive organs	(1,298)	
18	Malignant neoplasms of respiratory system	(1,144)	
19	Malignant neoplasms of breast	(3,813)	
20	Malignant neoplasms of genital organs	(1,736)	
21	Malignant neoplasms of urinary organs	(178)	
22	Malignant neoplasms of all other and	(2,229)	
23	leukemia	(789)	
24	Other malignant neoplasms of lymphatic system	(803)	
25	Benign neoplasms, carcinoma in situ	251	0.5
26	Diabetes mellitus	870	1.9
27	Nutritional deficiencies	24	0.1
28	Anemias	175	0.4
29	Meningitis	40	0.1
30	Major cardiovascular diseases	6,508	14.1
31	Diseases of heart	(4,489)	
32	Rheumatic fever and rheumatic heart	(220)	

Table 1.  
**Deaths Among U.S. Females 15 to 44 Years, All Races, by Disease Group  
 1988**  
**(continued)**

Group	Cause of Death	Number of Deaths	Percent
33	Hypertensive heart disease	(237)	
34	Hypertensive heart and renal diseases	(23)	
35	Ischemic heart disease	(1,579)	
36	Acute myocardial infarction	(965)	
37	Other acute and subacute forms	(22)	
38	Angina pectoris	(3)	
39	Old myocardial infarction and other diseases of endocardium	(589)	
40		(146)	
41	All other forms of heart disease	(2,284)	
42	Hypertension with or without renal disease	(95)	
43	Cerebrovascular diseases	(1,681)	
44	Intracerebral and other intracranial conditions	(519)	
45	Cerebral thrombosis and unspecified cerebral embolism	(82)	
46		(6)	
47	All other and late effects of cerebral arteriosclerosis	(1,074)	
48		(17)	
49	Other diseases of arteries, arterioles	(226)	
50	Acute bronchitis and bronchiolitis	10	0.0
51	Pneumonia and influenza	901	2.0
52	Pneumonia	(882)	
53	Influenza	(19)	
54	Chronic obstructive pulmonary diseases	523	1.1
55	Bronchitis, chronic and unspecified	(31)	
56	Emphysema	(28)	
57	Asthma	(377)	
58	Other chronic obstructive pulmonary diseases	(87)	
59	Ulcer of stomach and duodenum	58	0.1
60	Appendicitis	19	0.0

**Table 1.**  
**Deaths Among U.S. Females 15 to 44 Years, All Races, by Disease Group**  
**1988**  
**(continued)**

<b>Group</b>	<b>Cause of Death</b>	<b>Number of Deaths</b>	<b>Percent</b>
61	Hernia of abdominal cavity and intestines	54	0.1
62	Chronic liver disease and cirrhosis	1,337	2.9
63	Cholelithiasis and other disorders of gallbladder	38	0.1
64	Nephritis, nephrotic syndrome, and nephron	312	0.7
65	Acute glomerulonephritis and nephrotic syndrome	(7)	
66	Chronic glomerulonephritis, nephritis	(42)	
67	Renal failure, disorders resulting from	(263)	
68	infections of kidney	37	0.1
70	Complications of pregnancy, childbirth	328	0.7
71	Pregnancy with abortive outcome	(61)	
72	Other complications of pregnancy, including	(267)	
73	congenital anomalies	599	1.3
74	Certain conditions originating in	10	0.0
75	birth trauma, intrauterine hypoxia,	(2)	
76	other conditions originating in the	(8)	
77	symptoms, signs, and ill-defined conditions	1,598	3.5
78	Accidents and adverse effects	10,618	23.0
79	Motor vehicle accidents	(7,901)	
80	All other accidents and adverse effects	(2,717)	
81	Suicide	3,263	7.1
82	Homicide and legal intervention	3,520	7.6
83	All other external causes	470	1.0

Source: National Center for Health Statistics, Centers for Disease Control; compressed mortality file via WONDER, CDC's online public health information system. Eighty-three groups were selected; deaths totaled 46,129.

This report focuses on the following areas of emphasis for research: STDs (including HIV infection), reproductive morbidity, injuries, malignancies, and cardiovascular diseases.

## **Major Themes**

Several general considerations are fundamental to productive research in each of these emphasis areas. These include, but are not limited to, racial/ethnic issues, biobehavioral issues, and social context issues.

## **Racial/Ethnic Issues**

Inherent in any compilation of women's health research priorities is the fundamental assumption that a full array of racial/ethnic issues must

be addressed. Study samples should always include sufficiently large numbers from the major ethnic/racial groups to allow analyses of the effects of ethnic/racial characteristics. In addition, specific studies that focus on those conditions that disproportionately afflict minority women (e.g., systemic lupus erythematosus [SLE] or STD and HIV infection in Black and Hispanic women) must be a major priority.

Societal factors, as well as individual behaviors, are critical to the development and progression of a broad spectrum of diseases in both sexes. In women, the leading causes of mortality clearly highlight the need to complement biomedical investigations with behavioral research. As mentioned above, the status of women in subsegments of our society may make them particularly vulner-

**Table 2.**  
**Deaths and Death Rates for the 10 Leading Causes of Death by Sex and Race, Ages 15-44,  
United States, 1988\***

	Male				Female			
	White		Black		White		Black	
	Deaths	Rate	Deaths	Rate	Deaths	Rate	Deaths	Rate
Unintentional injury	25,901	52.9	4,139	59.5	7,967	16.5	1,211	15.8
Suicide	11,993	24.5	1,253	18.0	2,909	6.0	254	3.3
Heart disease	9,139	18.7	2,891	41.6	2,852	5.9	1,558	20.3
Cancer	8,602	17.6	1,712	24.6	9,703	20.1	2,121	27.7
AIDS	6,552	13.4	2,683	38.6	411	0.9	597	7.6
Homicide	5,791	11.8	6,964	100.2	1,882	3.9	1,527	19.9
Liver disease and cirrhosis	2,405	4.9	841	12.1	833	1.7	438	5.7
Cerebrovascular disease	1,269	2.6	649	9.3	1,069	2.2	569	7.4
Diabetes mellitus	975	2.0	309	4.4	628	1.3	229	3.0
Pneumonia and influenza	974	2.0	570	8.2	564	1.2	318	4.2

\* Rates per 100,000 population.

**Table 3.**  
***Complications of Sexually Transmitted Diseases and Women's Health***

Complication	Annual Incidence
Pelvic inflammatory disease	1,000,000
Infertility	150,000
Ectopic pregnancies*	44,000
Congenital infections	100,000
Cervical cancer	50,000

\*Main cause of pregnancy-related deaths in Blacks.

able to psychological illness or to violence. Furthermore, perceived or real limitations in access to health care may be greater for women than for men and may prevent early detection and treatment. Research initiatives specifically directed to women's health should consider new models that examine the two-way influence between behavioral and biological factors in an attempt to understand the impact of cultural and sociodemographic variables on health status.

Social context variables should include socioeconomic and sociopolitical factors, gender role issues, and access to health care (both overtreatment and undertreatment issues). These considerations are particularly important for research on the health of

minority women. They are essential to the development of culturally sensitive and culturally relevant interventions.

### ***Key Issues/Research Recommendations***

#### **STDs—Including HIV Infection**

Prevention and control of STDs, including HIV infection, are fundamental to the health of women and their infants. For both behavioral and biological reasons, these are diseases that disproportionately affect women, particularly disadvantaged minority women. Many STDs, including HIV infection, are transmitted more easily from men to women than from women to men. If infected, women are more frequently asymptomatic, and they are thus less likely to perceive a need to seek care. Even if symptomatic, women with STDs often do not present for care because these diseases in women are associated with tremendous stigma in many communities. Conversely, because double standards persist, an STD in a man is seen to represent either a coming of age or an amusing mishap. Among those women who do seek care, it is more difficult to detect most of the common STDs than it is in men. And the most common complications of STDs in women, which include infertility, tubal pregnancy, anogenital cancer, fetal loss, low birth weight, and congenital or perinatal infection, are more frequent and more severe than those that develop in men. Finally, because many women do not have complete control over when, where, or how they have sexual intercourse, they cannot protect themselves from STDs or their consequences.

**Table 4.**  
***Selected Sexually Transmitted Diseases in the United States: Estimated Annual Costs***

Syndrome	Cost	Source
Genital and neonatal herpes	\$68 million	Institute of Medicine, 1985
Gonococcal infection and sequelae	936 million	Institute of Medicine, 1985
Chlamydial infection and sequelae	2.2 billion	Centers for Disease Control, 1987
Pelvic inflammatory disease and sequelae	4.2 billion	Washington, et al., 1990

STDs can occur at any time during a woman's life, but their incidence tends to peak between the ages of 15 and 40 years. The magnitude of the STD problem in America is staggering in terms of both disease burden and cost (Tables 3 and 4). Each year, approximately 6 million women in the United States acquire an STD. Currently, roughly 3 million teenagers are infected with STDs. Annually, an estimated 2 1/2 million women acquire genital chlamydial infections, and 500,000 women acquire gonorrhea.

Due to delays in diagnosis or inadequate therapy, between 10 and 40 percent of women with gonococcal and/or chlamydial cervicitis, and a significant proportion of women with bacterial vaginosis, develop pelvic inflammatory disease (PID). Up to 1 million American women are diagnosed with PID annually; the total health care cost for PID in 1990 was more than \$4.2 billion. It is likely that many more women go undiagnosed. Furthermore, if the incidence of PID remains constant, at the current rate of inflation the projected costs of PID and its sequelae for the year 2000 will be almost \$10 billion.

As a consequence of the scarring that follows PID, approximately 17-25 percent of women become infertile, 15-18 percent develop debilitating chronic pelvic pain, and 20-25 percent present with recurrent PID. These complications are particularly devastating because roughly 70 percent of women who develop PID are less than 25 years old, and 75 percent have not yet had a child. Tubal pregnancy, which is potentially fatal, is 6 to 10 times more common among women who have had PID than among those who have never had upper-tract infec-

***"Women bear a disproportionate share of the consequences of sexually transmitted diseases through complications such as pelvic inflammatory disease and sequelae such as ectopic pregnancy and tubal infertility."***

Gail Cassell, Chairman, Committee on Medical Biology and Immunology, American Society for Microbiology

tion. Tubal pregnancy is the leading cause of maternal mortality in Black women today.

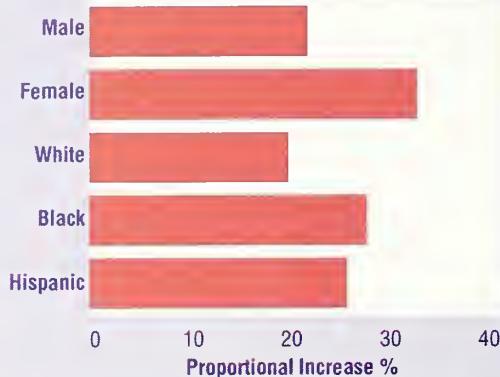
In the United States, it is estimated that 24 to 40 million people are infected with human papillomavirus (HPV). Genital infection with several biotypes of HPV is strongly associated with cervical cancer—which is one of the most common cancers among women in the developing world and which kills 5,000 American women annually.

The severe complications of STDs in infants adversely affect women's lives. Early fetal loss may occur in as many as 25 to 50 percent of women acutely infected with syphilis or genital herpes during pregnancy; low birth weight or prematurity may complicate a similar proportion of pregnancies in acutely infected women. Pregnant women with acute chlamydial or gonococcal infections, for example, are three to five times as likely to deliver a low-birth-weight or premature infant as are uninfected women. Congenital or perinatal infections occur in approximately one-third to two-thirds of infants of acutely infected mothers and may result in pneumonia, potentially blinding eye infection, or permanent neurological damage. The tripling in rates of infectious syphilis in Black women between 1984 and 1989 and the increasing rates among Hispanic women have resulted in a parallel epidemic of congenital infection in the United States.

As of October 1991, over 20,300 women with AIDS had been reported to the Centers for Disease Control (CDC), and an estimated 200,000 women may be infected with HIV. In 1990, the largest proportional increase in AIDS cases occurred among women (Figure 1). Nationally, AIDS is the fifth leading cause of premature death in women, and in several cities AIDS is the leading cause of death for women ages 15-49.

Finally, STDs and HIV infection are linked not only by common behavioral risk factors but also by biological interactions. The latter include both increased risk of HIV transmission in the presence of other STDs and altered natural history, diagnosis, and response to treatment of other STDs in the presence of HIV infection. Recent studies indicate that both ulcerative STDs (genital herpes, syphilis, and chancroid) and the more

**Figure 1.**  
**Increases in AIDS Cases Occurring Among Women**



prevalent nonulcerative STDs (chlamydia, gonorrhea, and trichomoniasis) increase the transmission of HIV at least three- to fivefold. Conversely, HIV infection may affect the course of several STDs. Data suggest that genital warts and genital ulcers may be altered in HIV-infected individuals: lesions may be larger, more persistent, or recur more frequently. Furthermore, complications of STDs such as syphilis and HPV infection may be more frequent or more severe, and standard therapy for syphilis, herpes, and chancroid may be inadequate in patients who are co-infected with HIV.

Priorities for STDs and HIV in relation to the health of women during this portion of the life cycle fall into five critical areas: disease patterns and mechanisms, diagnosis, treatment, vaccine development, and behavioral interventions. For clarity, the recommendations are listed here in five separate categories; however, in practice, many of the recommendations are interrelated and mutually reinforcing. Furthermore, it must be emphasized that the working group strongly endorses interdisciplinary approaches to research in STDs

and HIV infection, because these approaches provide a broad range of expertise that can contribute synergistically to the design and conduct of such research.

- Funding mechanisms and research infrastructure should be developed to facilitate collaborations among immunologists, microbiologists, protein chemists, and animal modelers within the area of basic research and, more broadly, among basic, clinical, epidemiological, behavioral, and operational researchers.

#### **Disease Patterns and Mechanisms**

- Understanding the nature of pathogen-cell interactions, especially the structure-function relationships that control attachment and entry of STD organisms in human cells is a prerequisite for the rational development of effective strategies to interrupt transmission of STDs. Continued research is needed to elucidate these basic mechanisms of acquisition of STDs and HIV.
- The mucosal immune system of the human female genital tract, its relationship to other mucosal immune systems, and its role in the prevention of STDs and HIV infection, should be studied. Specifically, antigen processing, humoral and cellular immune responses, and the effects of hormones on these responses should be examined.
- Research is needed to define the chronology and the host and pathogen factors involved in ascent of lower-tract organisms into the endometrium and Fallopian tubes and in subsequent development of tubal scarring. Development of improved animal models for PID would greatly facilitate this research.
- Seroepidemiological studies of infertile women and women with tubal pregnancies strongly suggest that atypical or subclinical PID is responsible for a substantial proportion of these disorders. The clinical and microbiological spectrum, the frequency, and the natural history of atypical PID should be determined.

- Future research should characterize the role of STDs in adverse outcomes of pregnancy. Factors such as chronicity of infection and stage of gestation during which infection occurs should be examined for specific pathogens. Improved understanding of the immunobiology of pregnancy and use of both natural and artificial animal models of STDs in pregnancy are likely to be important to productive research in this area. In addition, organisms should be examined for virulence factors or other markers associated with specific patterns of fetal or neonatal morbidity.
  - Both epidemiologic and basic studies are needed for a better definition of the risk factors and biological mechanisms that influence progression of HPV infection to anogenital neoplasia. HPV natural history studies that examine the roles of viral type and immune status are urgently needed. The molecular basis of latency and reactivation, and of initiation and potentiation of atypical cell growth, must also be clarified.
  - The role of STDs in HIV transmission should be further defined, with emphasis on those syndromes that, to date, have received little attention. These include gonorrhea, chlamydia, trichomoniasis, and HPV infection. Research on the reciprocal impact of HIV infection on the natural history, diagnosis, and response to therapy of other STDs in women is an equally high priority. This is particularly important with respect to PID and HPV infection. The pathogenic and immunologic mechanisms underpinning these STD-HIV interrelationships must be determined.
  - Prospective cohorts of women should be established to determine the clinical presentation and natural history of HIV infection in women. Factors that affect progression to AIDS should be identified, and the spectrum of opportunistic infections and neoplasms that occur in these women should be defined. Clinical, virologic, and immunologic markers of disease progression should be evaluated to female-specific end points.
  - Studies are needed to address the frequency and nature of factors responsible for HIV transmission to women and their infants. In addition to other STDs, these include stage of HIV disease, age, hormonal factors, cervical ectopy, and use of intravaginal preparations.
- Diagnosis**
- There is an urgent need for the development of simple, inexpensive, rapid STD detection methods that are accurate for both symptomatic and asymptomatic women. The highest priority in this area is the development of tests for chlamydial infection because of the complexity and cost of existing tests, the severe impact of untreated disease, and the availability of curative therapy. Development of analogous tests for viral STDs such as HSV, HPV, and HIV is also critical to control of these infections.
  - Improved methods are needed to diagnose PID and to identify women at high risk for its reproductive sequelae. Accurate, noninvasive approaches must be developed, particularly to address the challenges posed by atypical infections. Virulence factors and immunologic markers should be sought that are predictive of postinfectious infertility or ectopic pregnancy.
- Treatment**
- The most pressing research challenge in STD treatment lies in the development of curative antiviral agents for infections with HPV, HSV, and HIV. Studies are also needed to define better the effect of existing palliative therapies on transmission of these organisms and on progression of disease.
  - PID treatment regimens must be evaluated for their efficacy in preserving normal reproductive function, as well as for ability to achieve clinical and microbiological resolution of acute infection. This will require a multi-center clinical trial, with support for a minimum of 7 to 10 years, to permit adequate assessment of relevant long-term outcomes. The role of adjunctive PID therapy using anti-inflammatory or immunomodulating agents to reduce long-term consequences should also be examined.

- Further studies are needed to document the safety and efficacy of STD and HIV regimens during pregnancy.

### **Vaccine Development**

- Ongoing basic research on the microbiology, immunology, and pathogenesis of STDs is essential for the development of safe and effective vaccines. As indicated above, the mucosal immune system may provide important opportunities in the design of vaccines for STDs and HIV. Future research must also dissect the protective, neutral, and pathological aspects of the immune response to specific STD pathogens.
- Intensive efforts are under way in gonococcal, chlamydial, HSV, and HIV vaccine development. Resources should be made available to continue these efforts and to prepare for and carry out future vaccine trials.

### **Behavioral Interventions**

- Epidemiologic studies are urgently needed to identify the type and distribution of sexual and health care behaviors that alter the level of risk of STDs or their sequelae. Such information is essential to identify candidate behaviors and target populations for the development of intervention strategies, as well as to provide baseline data to assess intervention efficacy. A national survey of sexual and health-related behaviors relevant to STDs and HIV is strongly recommended. The recent cancellation of one such survey is scientifically unsound and should be reversed.
- Research is needed to identify the behaviors among health care providers that promote health care seeking, compliance with recommended regimens, and acceptance of vaccines by women.
- Gender-related barriers to prevention and care of STDs and HIV should be identified and interventions designed to help women overcome these barriers.
- To enable women to protect themselves from STDs and HIV infection, prevention methods that women can control themselves must be developed.

- Methodological research on the measurement of risk behaviors, and factors influencing the validity and reliability of such measurement, is urgently needed. Issues such as data collection, intervention characteristics, and instrument design should be examined in well-defined populations.

### **Endorsement of HIV Research Recommendations**

HIV infection is clearly of global importance. At present, the highest rates of increase in HIV incidence in the United States are among heterosexual women. As a result, in December 1990, a National Conference on Women and HIV infection was held. This conference issued a comprehensive set of research recommendations (see Appendix 6); the Young Adulthood to Perimenopausal Years working group fully endorses these recommendations.

### **Reproductive Morbidity**

High priority should be given to basic and applied research that can enable women of reproductive age to choose the timing and frequency of pregnancy. Specifically, research priorities must include the development of new safe, reliable, and convenient methods of fertility control. The short- and long-term effects of these methods must be evaluated and then monitored to ensure their safety and effectiveness. Also, the effect of hormonal modulation of steroid receptors on fertility regulation should be evaluated. Ongoing research efforts, as well as new initiatives, should be undertaken to develop new contraceptives for men. At the same time, the scope of research must be expanded to define the cause(s) of infertility and develop improved therapeutic modalities for alleviating this condition in women who want to become pregnant but are unable to do so.

Research also should focus on ensuring that each pregnancy can be carried to term without complication or risk to the health of the baby. Studies should determine the molecular-level events involved in parturition and the causes—and best means of prevention—of preterm birth. We also need to know what causes the complications of pregnancy that place a pregnancy (the mother, the fetus, or both) at risk. In particular, the hyper-

tensive disorders of pregnancy, premature rupture of the fetal membranes, and intrauterine growth retardation can threaten the life and well-being of both mother and fetus.

Studies also are needed to obtain data on a multitude of reproductive disorders in women that are not related to reproduction per se. Such studies will provide vital epidemiologic information and furnish key insights into the natural causes of various diseases. Some of these illnesses are: endometriosis, uterine leiomyomata, premenstrual syndrome, and chronic pelvic pain in women. Some of the facets of these disorders will be elucidated in studies on fertility; however, for some of these conditions, specifically targeted research will be required.

### **Fertility Control and Contraception**

The status of contraceptive development is sub-optimal. Surveys indicate that, at most, only 50 percent of those using currently available methods of contraception are satisfied with their method. In addition, the existing methods do not

***“The contraceptive methods currently available in the United States leave major gaps in the ability to control fertility safely, effectively, and in culturally acceptable ways.”***

*Marian Damewood, Associate Professor, The Johns Hopkins University School of Medicine, speaking for the American Fertility Society*

meet the needs of many individuals, including very young women, breast-feeding women, women with contraindications for use of the methods now available, and women attempting to protect themselves from STDs such as HIV infection. Thus, there is an urgent need for new, effective, inexpensive, and widely acceptable contraceptive methods that will give women a wider array of choices and also provide contraceptive options for men, lactating women, teenagers, and perimenopausal women.

Women also need contraceptives that will protect them against STDs.

- The long-term health effects of using both combination and progestin-only contraceptives should continue to be monitored, considering their possible involvement as factors in breast cancer, cardiovascular disease, and mood.
- Research is needed to develop improved hormonal implants that use levonorgestrel and other available progestins.
- New, safer oral contraceptives for women must be developed.
- Research should evaluate the efficacy and safety of immunocontraceptive vaccines.
- New, highly effective contraceptive barrier devices must be developed and evaluated.
- Studies should identify accurate, reliable, and inexpensive indicators of the preovulatory, ovulatory, and postovulatory phases of the female reproductive cycle.
- New antifertility drugs for men should be identified and evaluated.
- Research should identify new methods for sterilization that are potentially reversible and, perhaps, nonsurgical.
- Studies should continue to evaluate abortion technique, with an emphasis on the short- and long-term effects of abortion and the safety of the procedure.

### **Fertility and Infertility**

Currently, 1 married couple in 10 who want to have children is unable to do so. Infertility causes severe personal stress as well as a financial burden for these couples. Recent breakthroughs in medical therapy, microsurgery, and in vitro fertilization technologies can now ensure that approximately half the couples seeking to remedy infertility will achieve pregnancy; however, continued innovative and focused research on both the pathophysiology of infertility and the most effective treatments for it is needed.

- Epidemiologic studies should seek to define the causes of infertility and their prevalence, based on a large population study.
- Research should investigate new methods of diagnosis and therapy, particularly in the areas of unexplained or idiopathic infertility.
- Studies should analyze the biobehavioral aspects of infertility, including the study of attitudes toward an infertile woman or man and toward adoption.
- Treatment regimens should be developed that are targeted at sperm production and quality.
- Clinical trials are needed, based on well-formulated hypotheses for appropriate therapy.
- Studies should investigate what effects, if any, environmental toxins have on sperm and oocyte function and fertilization.
- Research is needed into the technology, biology, and relative success of medically assisted contraception. It is apparent that couples could benefit from such technology. Investigation of very early embryo-maternal cell signaling, as it relates to this new technology, is essential.
- Epidemiologic studies should be done to define normal fecundity and the relationship between natural fertility and age.

### **Pregnancy Loss**

Ideally, each pregnancy should occur when desired, proceed uneventfully to term, and result in a normal, healthy infant; but often, this is not the case. About 30 to 50 percent of conceptions are lost, some so early that the woman is not even aware that she has been pregnant. Three percent of infants will be born with severe malformations, and a much higher percentage of pregnancies terminate because of major chromosomal malformations and/or structural defects in the fetus.

It is likely that a significant portion of early fetal loss and developmental abnormalities is related to environmental factors. It has long been recognized that the use of drugs during pregnancy, either prescription or illicit, may adversely affect the fetus.

Successful reproduction requires synchronized interaction and precise timing, along with adequate function, at every level of the reproductive tract and central nervous system. Hormonally dependent changes in endometrial growth are required for successful implantation and pregnancy. Any alteration in this mechanism can result in loss of the pregnancy. In addition, some early losses, and perhaps some cases of premature birth, may be caused by an aberrant immune response of the mother toward fetal cells.

- Multidisciplinary research is needed to elucidate further the molecular and cellular mechanisms in normal and abnormal development.
- Epidemiologic studies should seek to gather data on deleterious environmental factors and work-related risks.
- The interactions between embryo and uterus that are essential to normal growth and development should be determined, and the effects of environmental agents on these processes should be assessed. The pathogenesis of adverse sequelae, including identification of the host factors that influence susceptibility and resistance, should be included in this research.
- Studies are needed on the development of the fetal immune system and its relationship to the maternal immune system.

### **Fetal Development and Growth**

More research is needed to ensure that each selected pregnancy is complication-free and culminates in the delivery of a healthy, normal baby. The emotional costs to families and the societal burden imposed by abnormal fetal development are immeasurable. While many congenital defects have their origin early in the first trimester of pregnancy, often before a woman realizes she is pregnant, growth and functional refinement of the fetal organ systems occur during the second trimester. Thus, throughout pregnancy, there are genetic and environmental factors that can adversely affect fetal growth and development, including prenatal infections and substance abuse (use of heroin, alcohol, and cocaine, as well as smoking). Furthermore, one of the major causes of profound, sometimes

lifelong, disability is preterm birth. Research on defining the causes of preterm birth and learning how to prevent it should receive major emphasis.

- A broad, multidisciplinary approach is needed for the study of fetal growth, including genetic, molecular, and cell biology; immunology; and physiology.
- Studies should investigate the fundamental aspects of placental function and fetal nutrition, including investigations into the mechanisms by which nutrients are transferred to the fetus from the mother.
- Continued research and controlled trials should be directed toward the development of techniques to diagnose and treat the fetus with genetic or anatomic abnormalities.
- Studies should investigate the mechanisms of maternal-to-fetal transmission of adverse infectious agents and the pathogenesis of defects resulting from congenital infections; strategies need to be devised to alter high-risk behaviors.
- Research should elucidate the biomolecular events involved in the maintenance of uterine quiescence throughout most of pregnancy.
- The relationship between infection and preterm labor should be investigated, as well as the mechanisms involved in premature rupture of the amniotic membrane.
- Studies should define the at-risk populations and measure the effectiveness of social and behavioral interventions in changing high-risk behaviors that impair and limit fetal development.

### ***Endometriosis***

It has been estimated that 1 to 5 percent of women of reproductive age have endometriosis, and as many as 45 to 50 percent of women suffering from infertility are affected by this condition. The morbidity associated with endometriosis, including pelvic pain, dysmenorrhea, and ovarian neoplasia (endometriomas), is significant, often necessitating surgical procedures such as hysterectomy and oophorectomy. Why some women with minimal dis-

ease have infertility, while others with significant disease do not, remains unknown. The natural history of early untreated disease is also unknown; why some women develop the disease and others do not is difficult to understand. Although there have been many years of attempts at treating endometriosis, the most appropriate treatment has not yet been determined.

- Studies should explore the natural course of endometriosis and the cause-and-effect relationship between this disease and infertility.
- Research should determine the etiology of endometriosis and determine why particular women develop this disease and others do not.
- Studies should establish the most appropriate therapy for this disease, ascertain which patients should receive therapy, and determine when treatment should optimally be initiated.
- Studies should analyze what role, if any, immunologic factors play in the causation of endometriosis.

### ***Uterine Leiomyomata (Myomas, Fibroids)***

The most common tumor of the uterus is the leiomyoma. It is estimated that up to 20 percent of all women over age 35 harbor uterine leiomyomata although, frequently, they have no symptoms. This disorder is a major cause of hysterectomy in women of reproductive age. In addition, leiomyomas may result in early fetal loss and in corrective surgery (myomectomy) for women who want to be pregnant.

- Epidemiologic studies, including those that consider racial differences, should elucidate the natural course of the disease.
- Biomedical research should examine the etiology of uterine leiomyomata and the effects of various hormones on neoplastic growth.
- Newer methods of management (perhaps non-surgical) should be explored.

### ***Chronic Pelvic Pain***

Pelvic pain is a common disorder, and when it persists for at least 6 months it is considered chronic.

Chronic pelvic pain may be secondary to a recognized disease process or to disturbed function of apparently normal organs. This condition can be devastating, interfering with normal family and work activities and frequently necessitating repeated surgical procedures, often without resolution of the underlying disease.

- Epidemiologic studies should define the etiology, pathophysiology, and natural course of chronic pelvic pain.
- Methods for effective management of chronic pain must be developed and evaluated in a diverse population.
- Studies should define the psychological issues associated with chronic pelvic pain and the most effective therapeutic regimens for this condition.

### **Premenstrual Syndrome**

Many women experience changes in mood and physical well-being prior to menstruation. The term "premenstrual syndrome" (PMS) is used to describe the disorder when the changes become so severe that they are distressing to the individual affected. The prevalence of PMS may be as high as 30 to 40 percent. The etiology is obscure: PMS may in fact consist of a group of clinical entities, and a multitude of etiologic factors may be involved. Nevertheless, in many instances the symptoms are sufficiently severe as to interfere with normal life functions and therefore necessitate treatment.

- Epidemiologic studies should define the prevalence, various etiologies, and natural course of PMS.
- Diagnostic criteria for PMS need to be developed.
- Research should define the psychological issues associated with PMS.
- Effective treatments for PMS need to be explored and evaluated.

### **Psychosocial Morbidity**

#### **Depression**

Depression is a common illness in the general population. The results of the Epidemiological Catchment Area (ECA) survey, which collected

information on the prevalence of psychiatric illness among 18,571 adults in 5 communities in the United States, showed that 6 of every 100 persons interviewed met criteria established in the *Diagnostic and Statistical Manual of Mental Disorders*<sup>1</sup> for major depression or dysthymia on a lifetime basis.<sup>2</sup> An additional 23 (per 100) reported that they had experienced 2 or more symptoms of depression on a lifetime basis. Depression is especially common among women: 5.7 out of every 100 women had experienced major depression, but only 2.7 out of every 100 men had; and similarly, 3.9 per 100 women had experienced major dysthymia, but only 1.9 per 100 men had. Women's excess risk for depression begins after puberty and continues throughout life, according to a recent Institute of Medicine report.

Depressive illness exacts a heavy toll in terms of loss of both social and economic functioning. Depression is a common precursor of suicide and, as such, is significantly associated with loss of life. Since depressive disorders are characterized by somatic symptoms, such as disturbances in sleep, body weight, and energy level, many people seek care for their "medical" problems. Thus, depressive disorders contribute to demands on the physical health care system.

Although diagnosis and treatment of depression have been the focus of much excellent research, women's excess risk for depression has not been adequately accounted for. Since this excess risk appears at puberty, it is assumed that it is related to hormonal events, but this assumption needs to be tested. Gender socialization may also be a contributing factor.

- Research should investigate why excess risk for depression emerges among women after puberty, along with the possible hormonal links and social concomitants of depression.
- The links between early childhood experiences and later depression need to be addressed, along with the connections between depression and substance abuse.

- Studies should determine appropriate treatments for those whose depression is complicated by a second diagnosis, such as substance abuse.

### **Substance Abuse**

The use of psychoactive drugs is common among the U.S. population. According to the National Institute on Drug Abuse's 1990 National Household Survey on Drug Abuse, 32 percent of women and 42 percent of men reported some lifetime use of illicit drugs. These statistics do not include the legal psychoactive drugs—tobacco, caffeine, and alcohol—all of which can lead to addictive disorders and secondary impairment of physical and mental health.

The gender gap still exists in terms of levels of drug abuse, but this gap has been narrowing in recent decades. Women may be particularly susceptible to advertising and media presentations of certain drugs, such as tobacco and alcohol, which link them to images of women's liberation; consider, for example, the slogan, "You've come a long way, baby."

The changing social patterns of drug use among women are closely linked to other social factors that structure their lives. For example, the crack epidemic has exacted a massive toll in some inner city areas but has hardly affected those residing outside of the urban ghetto. Heavy alcohol consumption is most likely to develop among women working in traditionally male-dominated sectors of the economy. In general, patterns of drug use reflect socioeconomic status, culture, and locale. All of these are shaped by market forces, as those who sell illicit drugs strive to increase their market share. The complex determinants of women's drug use are an important subject for future research and will contribute to establishing prevention programs.

Treatment of women's addictive disorders is a major area requiring research in the future.<sup>3</sup> We know little about the onset or course of addictive disorders in women. While it is clear that treatment programs designed for men do not seem appropriate for women, it is less clear what types

of programs will prove able to assist women in recovery. Also, many women with addictive disorders suffer from other problems, such as poverty and victimization, which must be attended to as part of the treatment program.

- Investigations should determine what factors explain the sharp increases in drug use among women and what prevention activities will be effective in light of these changes.
- Research is needed to understand how acculturation leads to increased incidence of illicit drug and alcohol use among Hispanic women.
- Researchers should investigate what programs can support the recovery of women during pregnancy.
- The links between substance abuse and trauma need to be explored. Research should examine how many substance abusers have a second psychiatric diagnosis, and what effect this "dual diagnosis" group should have on the organization of treatment programs.
- More research is needed on the kinds of programs and diagnostic instruments that are necessary: to improve diagnosis and treatment of female substance abusers and for women who have been highly stigmatized because of their use of drugs.
- Research should investigate the role of male partners and significant others in women's initiation, continuation, and progression of drug use.

### **Trauma**

Psychosocial and physical trauma significantly compromise the health of women during the young adult to perimenopausal years. The model shown in Figure 2 depicts the spectrum of antecedents and risk factors for events leading to physical and/or psychosocial injury; it demonstrates the physical and social environmental dimensions that interact with individual biological, developmental, and psychologic processes. The spectrum of events is broad, and those events that can be characterized as definable occurrences are emphasized. Many of these events can be prevented, along with many of the outcomes of those events

***"In the case of violent victimization, stress may be prolonged. Prolonged stress can cause not only changes in the endocrine system, but also in the immune and central nervous systems."***

Gwen Keita, the American Psychological Association

that do occur. If they are not prevented, the outcomes can at least be addressed in such a way as to reduce the likelihood that they will lead to future problems (e.g., use of drugs can lead to a car crash, which, in turn, can lead to posttraumatic stress disorder [PTSD], which can then lead to further drug use). While an awareness of the relationships among these areas is useful, psychosocial morbidity and injuries will be discussed separately in this discussion for the sake of clarity.

Research on women's psychosocial morbidity needs to measure the effects of class, ethnicity, and race, as well as the effects of gender roles and socialization. Such research needs to be cognizant of the multiple roles women occupy—as children, parents, wives, and workers—and of the ways in which their illnesses are generated from their interaction with their social environments. Finally, given the vast scope of recent changes in many communities, especially poor communities, research needs to sustain a broad perspective on the multiplicity of niches occupied by women in both sickness and health.

In the psychiatric literature, "trauma" is often defined as an event that is unusual or outside the range of ordinary human experience and highly stressful. Examples include rape, life-threatening accidents, and witnessing a murder. Both physical and sexual abuse are important categories of trauma that can occur in the lives of women and that may undermine their mental health. Victimization of women and its consequences for health during the remainder of their lives needs to be studied.

PTSD is an illness that may occur in the wake of a traumatic event.<sup>3</sup> Rates of PTSD measure the extremes of illness antecedent to trauma and so

provide a minimum estimate of the psychiatric morbidity that could be attributable to a traumatic event. Rates of PTSD in any group will vary with the rate of exposure to trauma, the background stress against which the trauma occurs, and the nature of the trauma. In a recent study of young adults in Detroit, Breslau and coworkers<sup>4</sup> found that 39 percent of young adults had been exposed to a traumatic event at least once in their lifetime. Of those who had experienced trauma, 24 percent had developed PTSD. Other findings from this important study are that 83 percent of those who had PTSD had one or more other psychiatric or substance use disorders in their lifetime, and personal assault and sudden injury affected both genders equally in terms of developing PTSD, but women were more vulnerable than men to developing the disorder when facing crises such as the sight of someone else being killed or seriously hurt or news of the violent death of a close relative or friend. Among women who had been raped, 80 percent developed PTSD.

Breslau and colleagues<sup>4</sup> point out the need for studies to demonstrate the effects of geographic and socioeconomic conditions on rates of trauma. In recent work with women who use crack cocaine and live in poor inner city neighborhoods, Fullilove and coworkers (unpublished data) found that 98 percent had experienced at least one traumatic event, and more than half had developed PTSD.

PTSD, in itself, may lead to the development of other illness. For example, 45 percent of those in the Detroit study who had PTSD also had a diagnosis of substance abuse. Similarly, comorbidity of substance abuse and PTSD is common among Vietnam veterans. Additional research is needed to clarify the relationship between traumatic and addictive disorders. Addictive disorders are not the only illnesses that may follow trauma; recent work by other researchers has found that childhood sexual and physical abuse are common among those diagnosed later in life with a mental health condition such as borderline personality disorder or multiple personality disorder. Because the research in this area is still in its early stages, we do not yet have an accurate assessment of the bur-

den of mental illness that might be attributable to the experience of traumatic events.

Physical and sexual abuse have special relevance for women. Women, who are usually smaller than men, are more susceptible to physical abuse. Also, women often have difficulty in obtaining support after the experience of victimization; in many typical accounts of suppressing a history of abuse, women who were sexually abused as children recount, "My mother told me to stop lying"; others who were beaten by their husbands relate that they were asked, "What did you do to make him so angry?" More recently, mental health practitioners and researchers have begun a serious "uncovering" of these experiences of abuse. Careful research in the field of trauma, highlighting—but not limited to—physical and sexual abuse, will undoubtedly reshape many current theories about the etiology and treatment of mental illness.

- Studies should determine the community-wide prevalence of physical and sexual abuse.

- It is important to find out if rates of abuse vary by community and, if so, what factors appear to influence these rates.
- Studies should determine what treatments are best for survivors of abuse.
- The links between experiences of abuse and other psychiatric illnesses need to be explored. Whether psychiatric illnesses differ according to what point in a woman's life she suffers abuse also should be studied.
- Research needs to investigate how the experience of abuse may shape a woman's functioning in intimate relationships.
- The kinds of training and diagnostic tools that can improve the diagnosis and treatment offered to survivors of abuse should be identified.

**Figure 2.  
Antecedents and Consequences of Injury Events: A Conceptual Model\***

Antecedents/Risk Factors	Events	Outcomes
Social stratification -racism, sexism, SES	Physical abuse/assault Sexual abuse/assault Motor vehicle crashes Drug ingestion War Natural disasters Fires Falls On-the-job injury Acts of oppression	Physical morbidity/mortality -injury -infection  Psychosocial morbidity -mental illness -addiction -long-term care -eating disorders
Social/environmental conditions -maintenance -natural disaster		
Hazard availability -drugs, weapons, toxins, infectious agents		
Individual characteristics -previous personal history -intoxication -occupation		

\*This is only a partial list of the many elements that may be involved.

## Injuries

***"In the United States, 1 death in every 12 is the result of injury. Severe injury is the leading cause of death up to the age of 44, and up to the age of 34 it kills more people than all other diseases combined."***

*Margaret F. Longo, American College of Surgeons*

In this discussion, unless otherwise noted, injuries include all forms of intentional and unintentional acute trauma such as motor vehicle crashes, drownings, poisoning, fires and burns, falls, and gunshot wounds. These events may occur in any setting—in the home, in the workplace, in vehicles, or during recreational activities.

Injury is the third overall leading cause of death in the United States and the leading cause among the population ages 1 to 44. Although the rates of injury are greater for males than for females at all ages, injury is the leading cause of death for females ages 1 to 37. In the 15-44 age group, injuries account for 35 percent of all deaths to women (compared with 50 percent of the deaths for males in the same age range). This translates to more than 17,500 total injury deaths annually among females in the 15-44 age group and 40,000 total injury deaths annually among females of all ages in the United States. For every injury fatality involving a 15- to 44-year-old woman, there are an estimated 715 medically treated injuries involving women of this age group (including patients who were hospitalized as well as those who received only outpatient care).

As a proportion of injuries among females of all ages, the 15-44 age group accounts for 42 percent of the deaths from injury, 48 percent of the morbidity (defined as hospitalization or use of medical care outpatient services) from injuries, and 51 percent of the lifetime costs.

Years of life lost from injury mortality versus other causes reflect the effects of injuries on the younger ages. For women, the average number of life years lost due to injury fatality is 35 years, while the comparable figure for heart disease is 11 years, and for neoplasms, 17 years.

Because of inadequacies in existing data systems, more is known about the characteristics of the injuries that result in death than those that are not fatal. This is an area that must receive special attention if we are to expand our knowledge about the nature of the injury problem in any segment of the population. According to 1986 death certificate data, the leading causes of fatal injury among U.S. women between ages 15 and 44 are motor vehicle accidents (37 percent of the injury deaths), homicide (19 percent), and suicide (19 percent). Although firearms are less likely to be used in homicides or suicides among women as compared with men, they are used in approximately 45 percent of all suicides among 15- to 44-year-old women and more than half of all female homicides. Police data indicate that about 30 percent of adult female homicide victims are murdered by a family member or acquaintance. To what extent these events represent the culmination of ongoing domestic violence is not clear, but one estimate is as high as 20 percent. In addition, homicides that occur at work are the major cause of occupational fatality for women, accounting for more than 40 percent of all occupational fatalities among the working-age population of women. If murders among women working in the home were included, the numbers would undoubtedly be considerably higher.

Motor vehicle injuries are most frequent among occupants of passenger cars. Higher rates of such injuries occur in rural settings, where crashes tend to happen at higher speeds. In approximately 70 percent of fatal nighttime crashes, female drivers are legally drunk (blood alcohol concentrations greater than or equal to .10 mg percent), compared with 80 percent for males. As with males, the risk to females of being involved in a fatal car crash is greatest between ages 15 and 24.

Mortality trends for all types of injuries reveal that the patterns of injuries for women are approach-

ing, and sometimes mirroring, those for men. While the overall rates for both men and women are declining, the rates for women are declining less rapidly than for men.

Patterns of injury requiring hospitalization differ from those for fatal injury. As with fatalities, these rates are higher among women ages 15-24 than those in the 25-44 age group. Motor vehicles are responsible for the largest share of the nonfatal hospitalization injuries to women ages 15-44. For the 15- to 24-year-old women, the second leading cause of injury-related hospitalization is poisoning; for 25- to 44-year-old women, the rates of hospitalization are higher for falls.

Because injury-related deaths occur at younger ages, the mortality costs, calculated over the life expectancy of the individual, are much greater than are those from other causes. For example, the per-person mortality cost for an injured female is nearly \$222,000, whereas comparable figures for heart disease and neoplasms are \$33,000 and \$85,000, respectively. Economic costs for injury vary by cause. For women in the 15- to 44-year-old age range, the total costs associated with injuries from motor vehicles are far greater than for any other type of injury. However, on a per-case basis, drownings (and near drownings) and injuries from firearms far exceed the costs for motor vehicle-related injuries. Among women ages 15-44, the average cost of injury for drownings/near drownings is roughly \$200,000; for injuries from firearms, the costs are in the range of \$30,000 to \$67,000 for these women. This is about 10 times the cost per person for injuries involving motor vehicles.

To address this range of issues, a broad research agenda is recommended. Increased attention should be paid to the role of the physical, social, and cultural environment in all phases of the injury/trauma continuum, as well as to applied intervention research aimed at preventing situations posing high risk for injury events and their outcomes. Better methods are needed for measuring, recording, and retrieving consistent and accurate information about the risks and both short- and long-term consequences of traumatic injury. Also, the scope of research on traumatic injury needs to be much broader; this can be accomplished by including a broad base of social science disciplines.

### **Risk Factors/Incidence Trends**

- Concentrated attention needs to focus on the role of alcohol use among women as a contributor to risk of injury. Analysis of trends should examine how women's drinking patterns have changed over time and how this is related to trends in injury occurrence. The role of advertising of alcohol for women should be scrutinized more closely, and efforts to reduce alcohol consumption and their differential effects among female populations should be targeted.

*"I would certainly like to make a plea for extending our interest well beyond the biomedical precursors of disease, and look at some of the societal influences on illness. For example, in the area of injury prevention, we are very much concerned about the advertising of alcohol being beamed toward women."*

*Susan P. Baker, Professor,  
Department of Health Policy and  
Management and Co-Director,  
Injury Prevention Center, The  
Johns Hopkins University*

- The impact of changing patterns of women's independence on driving behavior, exposure to driving-related hazards, and risks related to alcohol use should be explored.
- Patterns of work that might put women at risk for on-the-job homicide should be examined carefully, with particular emphasis on strategies to ensure that workplaces and work schedules provide maximum protection for female employees.
- As a means for developing interventions across settings and for all populations, the positive effects that the presence of female workers can exert on workplace safety should be studied more carefully.

- Research needs to examine suicide patterns more closely to address, among other issues: why the suicide rate for Black women declines after age 35 but continues to rise for white women until it peaks at ages 45-54; how increased firearm use by 15- to 19-year-olds has been a factor in increased suicide rates; whether suicidal threats and expressions of depression in women are taken less seriously than in men; and whether the most appropriate preventive actions are being used by health professionals.
- Studies should determine what factors have influenced the rise in homicide against women ages 25-34 in the past decade, when rates for males were decreasing. Misogyny is an important factor to consider in rising homicide rates for women.

### ***Interventions***

- The effectiveness of current strategies to reduce suicide, homicide, and domestic violence must be carefully evaluated (e.g., suicide hot lines, warrantless arrest laws).
- Better interventions to reduce injuries of all types need to be developed and implemented through national, state, and local policy initiatives, as well as through efforts directed at communities and individuals throughout the life cycle.
- The role of the mass media in setting the public's agenda for injury control needs to be more carefully assessed, with attention to the role of the press in reporting injury events and to portrayals of hazards or injury prevention in television programming.
- Improved methods to understand and modify the means by which risk information is communicated to policy-makers and the public must be developed, to facilitate better understanding of the injury problem and optimal strategies for prevention.
- Exercise and diet in the young adult and menopausal years influence bone loss, a major determinant of one important type of injury in older women—fractures. Research should address how exercise and dietary patterns can be modified in these important earlier years.

### ***Women as Family Members***

- The role of women's work and its effects on child safety should be studied in the context of the relative risks to children associated with various child care settings and the anxiety about access to quality child care that troubles many working women.
- The effect on women's health from assuming all, or most of, the work in the home, while also working outside the home, needs to be studied.
- Greater understanding is needed about the reasons women purchase firearms and the conditions under which they are stored and used. Of particular interest are gun ownership and use patterns in female-headed households where desire for protection and risks to children may both be substantial.
- The impact of long-term disabling injuries to women should be studied in the context of economic and social/emotional hardships for families of disabled women.
- The impact of injuries to other family members should be studied in view of its effect on female caretakers to these injured persons. Families who have lost a provider to death should be studied for the effect on surviving female caretakers (e.g., effects of Black male homicide upon Black families).

### ***Surveillance/Measurement Issues***

- Morbidity surveillance must be improved so that an accurate measurement of causes of injury for both inpatient and outpatient visits is possible. One strategy is to require that information about external cause of injury ("E codes") be included on all routine reporting forms. Another is to ensure training in E coding for all personnel responsible for medical records in emergency departments and inpatient records departments. Also, clinicians should be certain to elicit adequate information from patients about the circumstances of injury and include this information in the medical history.
- Mechanisms must be developed to ensure that data linkage among data systems for morbidity and mortality is possible.

- Improved systems of recordkeeping need to be implemented to monitor injuries in the workplace. These systems should be sensitive to specific issues associated with female workers, such as including a mechanism to code on-the-job injuries for women working in domestic situations, in part-time jobs, or in other settings not regulated by the Occupational Safety and Health Administration.
- More accurate measures of domestic violence, suicide, and on-the-job injury need to be established.
- Death certificate reports of poisoning need to distinguish between intentional and unintentional cases.

## Malignancies in Reproductive-Age Women

Although cancer is a leading cause of mortality in women ages 15 to 44, the actual incidence is rather low for this age group when compared with women ages 45 to 84. Specific incidence rates are presented in the chart below.

Because of the relatively low number of cancers diagnosed in women of this age group (15-44) as compared with older women (45-84), it is appropriate to consider preventive interventions and early disease diagnosis rather than treatment strategies. There are four broad strategies that should yield significant positive results for the health care of women ages 15 to 44. Disease prevention may prove to be the most effective strategy, since the numbers of cases of cancer diagnosed in this age group are relatively low. Lifestyle alterations and the use of oral contraceptives during the reproductive years could potentially decrease the incidence of breast, endometrial, and ovarian cancer. Early disease detection through breast and cervical screening is of proven benefit in reducing mortality and morbidity associated with breast and cervical cancer. However, a significant number of women do not undergo these tests at recommended intervals. This issue has been addressed in *Healthy People 2000: National Health Promotion and Disease Prevention Objectives*. Research is needed to identify why women and health care providers do not follow current screening guide-

lines and to find effective ways to increase compliance with current guidelines.

Finally, improved treatment strategies are desperately needed. These will rely on a better understanding of the events that contribute to tumor initiation and promotion at the molecular and cellular levels. It is also crucial that efforts directed at new drug development continue.

### Breast Cancer

Breast cancer is the most common form of cancer in women. It has been estimated that one woman in nine in the United States will develop breast cancer during her lifetime.

Breast cancer is a heterogeneous disease; a single, unifying hypothesis applicable to all cases has not been formulated. Parity, lactation, and delayed menarche exert a protective effect. Caffeine and alcohol do not appear to increase risk, whereas the effect of diet remains controversial. The effect of maternal use of diethylstilbestrol (DES) on subsequent development of breast cancer has not been determined.

*“If all women over age 50 had regular mammograms, the death rate from breast cancer in this country would drop by one-third.”*

Luella Klein, American College of Obstetricians and Gynecologists

A family history of incidence definitely increases the risk, as does a prior diagnosis of colon cancer or endometrial cancer.

- Studies should determine the role of oral contraceptives upon later risk of breast cancer.
- The fact that only one case of breast cancer out of four can be accounted for by known risk factors indicates that additional epidemiologic studies are warranted.
- Studies should be continued on DES-exposed mothers and their offspring.

***Cancer Incidence Rates (per 100,000 women)***

Site	15-19	20-24	25-29	30-34	35-39	40-44
GI tract	0.5	0.8	1.9	4.4	9.0	19.2
Colorectal	0.1	0.3	0.9	2.6	5.5	12.9
Lung	0.2	0.3	0.7	1.3	4.2	15.4
Breast	0.0	0.8	7.4	26.7	86.2	129.4
Female genital tract	2.7	4.7	11.9	19.8	30.2	43.0
Cervix	0.5	1.8	7.2	11.9	15.9	16.8
Uterus	0.0	0.1	0.8	2.6	6.5	12.3
Ovary	1.1	2.2	3.2	4.1	7.1	11.6

Breast cancer is considered a hormonally dependent neoplasm: almost all aspects of the normal development and differentiation of the mammary gland are under multihormonal control. The mechanisms by which normal mammary tissue becomes malignant are largely unknown, although numerous clues continue to emerge from ongoing molecular biologic studies. Once established, localized hormone-dependent tumors often become resistant to hormonal manipulation, although the mechanisms by which this occurs are also largely unknown.

The prognosis for women with breast cancer is based on a consideration of multiple factors, although there is no generally accepted definition or prognostic model. The single most important indicator is axillary node status and, when present, the number of nodes. Other clinical prognostic indicators include standard staging, histopathologic features, and hormone receptor status. A variety of histopathologic factors have been associated with a poor prognosis.

- Improved treatment strategies for breast cancer are imperative, as evidenced by the statistic that the 5-year survival rate for women diagnosed with breast cancer during the period 1981-87 was only 78 percent.
- The surgical management of breast cancer requires ongoing scrutiny.

The necessity for mastectomy at the early stage of breast cancer must be questioned, given the excellent survival rates achieved by lumpectomy and radiation therapy. The NIH Consensus Development Conference provided guidelines for the treatment of women with early-stage breast disease, but these recommendations have been criticized because they excluded women over the age of 70 and those with small cancers in which the receptor status was unknown; and women with stage I and II cancers were combined and considered as a single group.

Adjuvant therapy reduces relapse rates and prolongs survival. For premenopausal women, the current treatment is multidrug therapy for 6 months and tamoxifen or short-term chemotherapy; for postmenopausal women, long-term tamoxifen. Endocrine therapy has emerged as a major treatment for early-stage disease. At present, a clinical trial is being conducted in Europe to determine the efficacy of prophylactic tamoxifen therapy in reducing the incidence of breast cancer. There are some problems with this study, however, including the potential risk of liver cancer, uterine cancer, and cardiovascular disease.

The issue of hormone replacement therapy for these women, particularly women 15 to 44 years of age, is very important, since relatively large numbers of women are diagnosed with early-stage

disease and can be expected to live for prolonged periods of time. At this time, estrogen therapy is believed to be contraindicated, yet the scientific information to support this supposition is actually quite limited.

- Well-designed studies must answer the question of the safety of hormone replacement therapy in women diagnosed and treated for breast cancer.

### **Lung Cancer**

Neoplasms of the lung have increased alarmingly in women, paralleling an increase in cigarette smoking.

- Cigarette smoking remains the single most important risk factor in lung cancer, so research efforts into interventions to change this behavior are appropriate.
- Currently, there are no cost-effective screening strategies for lung cancer. Few patients are cured by surgical resection, largely because the disease has usually reached an advanced stage at diagnosis. Treatment strategies generally employ combination chemotherapy and radiation therapy. Continued research in treatment strategies is warranted.

### **Colorectal Cancer**

Colorectal cancer is not a particularly common neoplasm in women of this age group. Numerous studies suggest a relationship between colon cancer and diet, yet this remains a controversial subject that merits further study.

The screening method recommended for colorectal cancer (sigmoidoscopy) is not widely accepted by patients nor advocated by most physicians, based upon practice audits.

- Continued research to identify additional screening tests for colorectal cancer that are acceptable to patients and physicians are warranted.

### **Cervical Cancer**

Although cervical cancer is not a major problem for women of this age group, the prevalence of preneoplastic lesions is increasing among these women.

The etiology of cervical cancer, particularly squamous cell cancer, has been associated with multiple sexual partners, initiation of sexual activity at an early age, cigarette smoking, and a history of STDs. The effect of certain dietary deficiencies as a risk factor for cervical dysplasia is currently a subject of debate. Alterations of the host immune system also appear to be important: chronically immunosuppressed women, such as renal transplant patients, are at significantly increased risk of developing cervical cancer. Recently, concern has been expressed that women with HIV infection and AIDS patients may also be at increased risk of cervical dysplasia and neoplasia.

Recent trends clearly demonstrate a decline in the number of cases of invasive cervical cancer diagnosed during the past 10 years, with a concomitant increase in the number of cases of preinvasive disease. This has been attributed to improved screening with the Papanicolaou test. Unfortunately, there are still groups of women who do not avail themselves of periodic Papanicolaou tests. In addition, there is considerable controversy in the literature concerning optimal screening intervals and the appropriate duration of cervix screening.

During the past decade, increasing attention has been focused upon human papillomavirus (HPV) as an important cofactor in cervical pathology. Currently, HPV infections of the lower genital tract are occurring in epidemic numbers, although precise statistics are not available. And no fully effective treatment strategies for this infection exist, even though it is an area of intense clinical interest.

Radiation therapy is the mainstay of treatment for all stages of cervical cancer. Because the infield failure rate increases with stage of disease, there has been increasing interest in the development of radiation and hypoxic sensitizers. To date, only hydroxyurea—in addition to radiation therapy—has conferred a survival advantage for patients with stage III cervical cancer. Various combinations of chemotherapy have been tested, but an increase in response or survival has not been demonstrated consistently. Hyperthermia as an adjunct to radiation therapy is currently being investigated as a new treatment strategy.

Except for those women who develop a recurrence in the central pelvic area that is amenable to surgery, recurrent cervical cancer following radiation therapy is fatal. Cisplatin remains the single most active agent for recurrent cervical cancer, but the response rate is only 30 percent, and reports of cures are merely anecdotal.

- Research should identify improved treatment strategies for cervical cancer. Survival, considered stage for stage, has remained largely unchanged for the past 50 years.
- Studies should identify new curative treatments for HPV infection.

### ***Uterine Cancer***

Uterine cancer is the fourth most common cancer in women. There is evidence that the age-standardized incidence rates for endometrial cancer are rising, although the reason for this is not clear.

The etiology of adenocarcinoma of the endometrium, which is the most common uterine neoplasm, has not been established. Epidemiologic studies have demonstrated an association between infertility related to anovulation, upper-body obesity, and age at last delivery. These factors all increase exposure to unopposed estrogen and appear to contribute to the development of good-prognosis, estrogen-dependent neoplasms that exhibit well-differentiated lesions with limited myometrial invasion and a low incidence of retroperitoneal pelvic node metastases.

Although unopposed estrogen appears to play a role in the etiology of some endometrial cancers, this model is not universally applicable. Differences at the molecular biologic level have been identified among neoplastic, hyperplastic, and normal endometrium and should provide insights into the initiation and promotion of these lesions.

The diagnosis of endometrial cancer is usually made after the onset of vaginal bleeding in a postmenopausal woman. There has been some interest in the development of vaginal ultrasound as a screening test for uterine cancer.

Surgery remains the mainstay of therapy for uterine cancer. Adjunctive radiation therapy is reserved for patients with high risk or metastatic

disease. Metastatic and advanced stage disease may be treated with a variety of chemotherapeutic agents. Adriamycin and cisplatin exhibit a dose-response relationship and appear to be the most active single agents. Progestins have also been used in the treatment of recurrent endometrial cancer, with a response rate of about 30 percent for a median duration of 10 to 12 months.

- The issue of hormonal replacement therapy for women diagnosed and treated for endometrial cancer remains controversial largely because of the small series reported to date. This area requires further investigation.

### ***Ovarian Cancer***

***"Ovarian cancer has been and remains a lethal disease, and the number of new cases is on the rise. On the national level, 20,500 new cases of ovarian cancer were diagnosed last year [1990], and 12,400 women died from the disease.***

***Today, ovarian cancer is the second most common gynecological malignancy, surpassed only by endometrial cancer. And it kills more women than all other gynecological malignancies combined."***

*Irma E. Goertzen, President,  
Magee-Womens Hospital*

Ovarian cancer is the most lethal of the gynecologic malignancies. Most ovarian cancers are of epithelial origin, although women 15 to 25 years of age are more likely to develop germ cell tumors. In general, ovarian cancer is a disease of postmenopausal women.

The risk factors for ovarian cancer are poorly defined, although the role of heredity is receiving increasing attention; the familial ovarian syndrome and Lynch syndrome II are two well-recognized entities.

Ovarian cancer screening is a topic of great interest not only to clinicians, but to the lay public as well. At this time there are absolutely no data to suggest that ovarian cancer screening should be adopted as public health policy, although there is increasing pressure from certain groups to do so. This is an area that must be investigated to avoid the widespread use of a practice that is not helpful and could in fact be harmful.

The treatment of ovarian cancer begins with aggressive surgical therapy, followed by combination chemotherapy. Currently, platinum-based regimens produce a response in 60 to 80 percent of women, but less than 10 percent of these women survive for 10 years.

- There is a pressing need for more effective therapies for ovarian cancer. There is considerable interest in using taxol, although this drug is only available in very limited amounts, and efforts to synthesize it have been unsuccessful to date.

## **Cardiovascular Disease**

During the 20 to 30 years that represent the young adult to perimenopausal period, women are at far lower risk for cardiovascular disease or disability than later in life. However, heart disease and cerebrovascular disease together constitute the third most common cause of death in women of this age group. In addition, the lifestyle choices made, as well as insults to health produced by diseases known to be coronary risk factors, contribute to the development of early coronary atherosclerosis during these years. Thus, this is a critical period for implementing preventive measures in hopes of altering later outcomes. Lifestyle factors including diet, exercise, and smoking, as well as conditions such as obesity, hypertension, and diabetes, are areas of particular concern.

- Studies of cardiovascular diseases in women should take advantage of both current knowledge about these illnesses in men and epidemiologic studies already in progress to focus on the mechanisms of this disease. This is especially important in light of the primacy of preventive measures in this age group, when disease can be developing and is often subclinical. In addition, such information might permit addressing

***“There is a large body of evidence indicating that in coronary heart disease we are dealing with a chronic disease process which evolves over a long period of time. The sequelae of heart disease in women usually don’t become manifest until after menopause. The most effective biomedical intervention is early recognition of risk and initiation of prevention strategies in younger, premenopausal women.”***

*Patty Looker, Executive Director,  
The National Association of  
Women’s Health Professionals*

several diseases at once—both scientifically, since pathophysiologic processes are often interconnected, and clinically, since lifestyle interventions often improve overall health as well as prevent specific diseases.

- Future research should focus on the particular risk factors for coronary heart disease in women, since evidence suggests these may be different, or of variable importance, compared with those for men; how risk factors can be modified; and whether such modification can alter morbidity and mortality. This is particularly important for “established” risk factors, such as lipoproteins, which are considered by both the public and the scientific community to be primary targets for preventive and therapeutic interventions.
- Future considerations of cardiovascular disease in women must begin with a broader understanding of gender differences in cardiovascular health by addressing normal female physiology. Evidence suggests that myocardial and vascular structure and function in women differ from those in men.

- Other physiologic factors associated with cardiovascular risk, which are known to affect a variety of disease states, include intra-abdominal fat (regional adiposity) and hyperinsulinemia/insulin resistance. These entities merit further attention because they are likely to provide keys to better understanding the pathophysiology of coronary heart disease, hypertension, and diabetes, and also because interventions directed toward improving them may have multiple positive effects.
- A sedentary lifestyle has been linked to development of atherosclerotic coronary artery disease, osteoporosis, and malignancy, among other disease states. Research is needed to explain the mechanisms for such relationships.
- Description of the normal physiology of physical activity in women, including the acute and chronic effects of exercise in the normal state and in pregnancy, is limited. Since the potential healthful effects of this nonpharmacologic intervention are so broad, particular attention should be directed to better understanding the physiologic changes associated with it.
- The female physiologic environment, and its impact in the pathophysiology of subsequent disease states and their treatment, must be delineated.
- Similarly, racial differences must be explored.
- There is also evidence that cardiovascular risk is increased in women with polycystic ovary syndrome. This association must be explored. In one small study of 257 unselected women, 23 percent had polycystic ovary syndrome.<sup>5</sup>

Structural heart disease in women of this age group is relatively uncommon, with the exception of mitral valve prolapse (MVP). However, the true prevalence of clinically important myxomatous degeneration is unclear, as are its consequences in women as opposed to men.

Pregnancy carries a variety of cardiovascular health risks related to both preexisting heart disease (primarily congenital and valvular) and cardiovascular

conditions arising from pregnancy itself, such as eclampsia. Although common, and a major health risk in this age group, cardiovascular considerations are poorly understood, and therapy is usually empirical.

Congenital heart disease is an increasingly common finding in the adult population, many of whom have significant residual disease or disability. Diseases related to vascular reactivity are more common in young women and include such common entities as migraine headaches and Raynaud's phenomenon but may also extend to the different manifestations of hypertension in this patient population, as well as to the syndrome of anginal chest pain in the absence of fixed coronary artery disease.

Some forms of thrombotic disease are more common in women, including deep venous thrombosis, pulmonary embolism, and a rare entity, primary pulmonary hypertension. The risk of thrombosis is substantially increased with use of birth control pills, a frequently used medication in this age group.

Psychosocial factors have been shown to affect atherosclerosis in animal models of coronary heart disease and have been recognized as important modulators of disorders such as hypertension and MVP in humans.

- Future research should explore the appropriate endocarditis prophylaxis for MVP and therapy for associated disorders such as arrhythmias, atypical chest pain, thromboembolism, and mitral regurgitation.
- The physiology and management of pregnancy in women with congenital heart disease deserve further study.
- Future research should be directed toward a better understanding of normal and abnormal cardiovascular physiology during pregnancy, the mechanism by which cardiovascular disease arises from pregnancy, and the treatment of cardiovascular conditions during this period.

- The gender-related differences in vascular physiology, as well as these clinical entities, should be examined and mechanisms and possible therapies explored.
- Gender-related differences in hemostasis and thrombosis should be examined, with particular reference to the diseases mentioned as well as coronary heart disease.
- The biobehavioral mechanisms of heart disease should be elucidated.

## **Special Issues**

To advance progress pertinent to these years of young adulthood to menopause will require increased collaboration among a variety of investigators, including immunologists, microbiologists, molecular biologists, experimental pathologists, epidemiologists, behavioral scientists, clinicians, and others. Funding, training mechanisms, and research infrastructure must be developed to facilitate and promote such collaborations.

Just as estrogen-receptor positive cancers respond to tamoxifen, progesterone-receptor breast cancers should, in theory, respond to an antiprogestin. This is one of the areas of inquiry related to the drug RU 486. RU 486 has been tested for a variety of hormonally dependent conditions. While it has *not* been shown to be effective in the treatment of glaucoma, premenstrual syndrome, and the more common forms of Cushing's syndrome (corticotrope adenomas), it does show promise in other areas.

In addition to the much publicized use of RU 486 as an abortifacient, the drug has other potential applications. Intramural researchers have shown that the maturation of the endometrium is delayed by a small daily dose of RU 486, an indication that it may have useful contraceptive properties. Ongoing studies are investigating the effect on cervical mucus and folliculogenesis. Related to the possible contraceptive effects of RU 486 on

the endometrium is the potential effect on endometriosis. As noted earlier, endometriosis affects 1 to 5 percent of women of reproductive age and may be associated with infertility. Since the endometrium is progesterone dependent, RU 486 might serve as an additional treatment option because current therapies have drawbacks, especially for women seeking pregnancy. The application of RU 486 to induce labor for term pregnancies might have considerable clinical value, but remains largely untested.

Meningioma tumors, which have estrogen and progesterone receptors, may also be susceptible to RU 486. As such, some tumors may be under sex steroid hormone control and, thus, a hormonal agent such as RU 486 might be efficacious. The Southwest Oncology Group, with a grant from the National Cancer Institute, is conducting a clinical trial using RU 486 in meningioma patients.

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## **PERIMENOPAUSAL TO MATURE YEARS**

*Cochairs:*  
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**T**he perimenopausal to mature years (ages 45 to 64) are unique in a woman's life, in part because of the occurrence of menopause. However, the fundamental biologic processes involved in menopause, as well as the full range of its consequences, are largely unknown at this point. Also, during these years many of the major chronic conditions first become manifest, and there may be changes in risk factor status that alter vulnerability to disease in later life. For these reasons, research on the middle years of a woman's life must be a high priority.

Many of the conditions that emerge during the perimenopausal to mature years are public health concerns; these include heart disease, cancer, arthritis, depression, disability, and injury. The prevalence of many of these conditions is high, and the rates of some increase markedly from the beginning to the end of this age span. These prevalence rates indicate the toll of the most lethal diseases. One out of seven women in this age range already has clinical heart disease; lung cancer is the leading cancer killer; and breast cancer is the second. One-third of U.S. women have had a hysterectomy by age 54, a much higher prevalence

than in most other industrialized societies. Approximately 3 percent of women in this age group have a major depressive episode.

*"The research agenda for women's health should be expanded to encompass women's health in all life stages, not primarily during the reproductive years. . . . Historically, the scope of women's health research has been too narrow."*

*Carol S. Weisman, Professor, The Johns Hopkins School of Hygiene and Public Health, speaking for the American Public Health Association*

There are also marked differences in the prevalence of these health problems in minority women. For example, diabetes, a major cause of morbidity, is two to three times more common in Blacks, Hispanics, and Native Americans than in whites. There are large gaps in descriptive data on major chronic conditions among minority women, as

well as obvious deficiencies in basic knowledge about the reasons for these documented differences.

Specifically, recent data show that, among white women ages 45-54, 32.3 per 100,000 population have coronary heart disease. Black women in this age group show a rate that is nearly three times as high as among whites—76.5 per 100,000 population. These rates climb dramatically for women ages 55-64—to 138.1 for white women and 243.5 for Black women. Conversely, data on Native Americans (from the 1987 National Health Expenditure Survey) reveal that only 1 in 10 women (more precisely, 10.1 percent) in this same age group has cardiovascular disease.

Breast cancer rates are slightly higher among white women than among Black women. For example, in women ages 60 to 64, rates per 100,000 population were 279.0 for Blacks versus 352.4 for whites. Conversely, rates for lung cancer are higher among Black women: for white women ages 45-49, 50-54, and 55-59, prevalence rates were 34.3, 55.5, and 113.3, respectively; for Black women in these age groups, the rates were 53.8, 89.7, and 135.9, respectively.

There is a relatively high prevalence of colon cancer among Black and white women ages 55-59: 57.4 and 71.8 per 100,000, respectively. This number rises sharply among Blacks in the age group 60-64 years, to 115.9 per 100,000—compared with 85.4 for white women ages 60-64.

Statistics on arthritis are not currently available by 5-year age group and racial/ethnic group. However, the 1989 National Health Information Survey estimated that the prevalence among all women ages 45-64 was nearly one in three—300.9 per 1,000 population.

The prevalence rates on osteoporosis climb steadily with each age group considered: 17.9, 39.2, 57.7, and 65.5 percent for women ages 45-49, 50-54, 55-59, and 60-64, respectively, in one study on women in Michigan. (In this group, the rate for those age 75 and older had reached 89.0 percent.)

Mental health problems also burden women in this age group. In a 1988 study of 1-month prevalence

rates among women in a five-site sample that constituted the National Institute of Mental Health Catchment Area Program, 3 percent of women ages 45-64 had had a major depressive episode, while 7.2 percent had experienced affective disorders of some type.

Diabetes is particularly common among women ages 45-64: 3.9 percent of white women 45-54 years old have diabetes; 5.8 percent of white women ages 55-64 have this condition. Rates are considerably higher among nonwhite populations. Among Black women ages 45-54, 8.3 percent are diabetic; this rate climbs to 14.2 percent among Black women 55 to 64 years old. Among Native American women ages 45-64, diabetes is extremely common: 21.8 percent have this disease.

The extent of disability among women ages 45-64 is difficult to quantify, because measuring its prevalence is highly dependent on the definition selected for disability. However, in examining U.S. Health Information Study data from 1990, which defined the most severe type of disability as the inability to carry on one or more major activities of daily life, researchers found that among women ages 45-64, this type of disability was present among 6.5 percent of white women, 11.4 percent of Black women, 9.3 percent of Hispanic women, and 12.9 percent of Native American women.

While menopause is the major physiologic event during this part of the life span, the perimenopausal to mature years also encompass major transitions in social roles and life circumstances for women. For example, a substantial number of women will be widowed or divorced during this period, increasing the possibility of social isolation. For women ages 45-54, the 1990 census data show that 5.3 percent are widowed and 14.4 percent are divorced. These changes may affect physical and emotional health. Consequently, study of their effects should be incorporated into the research agenda.

The confluence of physical and psychosocial changes that occur during this part of the life span necessitates that the concept of health should be broad and not limited to the absence of disease.

## Major Themes

The working group identified three high-priority themes under which specific research recommendations could be organized: understanding the effects of endogenous and exogenous estrogen on health; understanding the effects of behavior on health; and understanding differences in health status among socioeconomic, racial, and ethnic groups.

At the same time, working group members recognize that major changes have occurred in recent years that greatly influence nearly every aspect of women's lives; these changes may directly affect the health of women and include multiple social and work roles, biological influences (e.g., occupational and environmental exposure on the incidence of cancers), and interactions between biological and social factors (e.g., the interaction of biological changes in menopause and environmental stressors). However, the deliberations of this working group when considering these issues were tempered by the knowledge that attention was being afforded these issues by other panels—for example, see the discussion of the ramifications for mental health of a woman's social context in the report on Young Adulthood to Perimenopausal Years.

The major research recommendations under each of these themes are briefly described below.

## Key Issues/Research Recommendations

### Effects of Estrogen on Health

- Primary and secondary prevention trials should be done to assess the long-term risks and benefits associated with estrogen use. The trials should assess fractures, heart disease, breast and other female cancers, cognitive function, and quality of life as outcomes, as well as morbidity and mortality from all causes.
- Observational studies should be done to determine whether estrogen use and/or estrogen and progestin use increases the risk of breast cancer.

*"Perhaps the most immediate research question which I believe ought to be addressed is the issue of hormone replacement therapy in women past the menopause. . . . I am concerned that we will not have sufficient data to make those practice plans most beneficial to the women who will be taking those hormones."*

*John LaRosa, Chairperson, Task Force on Cholesterol Issues,  
American Heart Association*

- Studies should examine the transition from premenopausal to postmenopausal status, including the changes that occur in endogenous estrogen levels and in hormones other than estrogen.
- Research should elucidate the cellular and tissue-specific effects of estrogen and estrogen deprivation, particularly on bone, breast, and the cardiovascular system.
- Studies should delineate the mechanisms by which estrogen, progestin, growth factors, androgens, and neuropeptides may induce cell transformations and promote tumor growth.
- Research should develop and test alternatives to estrogen for treatment of perimenopausal symptoms and for the prevention of heart disease and osteoporosis in women for whom estrogen use is not appropriate.
- Studies should assess the effects of early menopause (whether chemically, surgically, or disease induced) in breast cancer survivors, as well as the effects of hormone therapy in this group. Of particular importance is the effect of hormone therapy on recurrence of breast cancer, the development of heart disease, and quality of life.
- Research should monitor the long-term consequences of in utero exposure to diethylstilbestrol (DES). A major reason for performing such follow-up studies is to alert women about increased

risk when there is compelling evidence and to reassure them about those outcomes for which the evidence is weak or absent.

## Behavior and Health

- Studies should identify successful interventions for long-term weight management, including interventions to increase physical activity levels.
- Research needs to determine optimum clinical decision-making strategies for women with common chronic conditions (e.g., cardiac conditions).
- Studies should identify the particular stressors that most influence women's health and the biologic concomitants of stress common to women.

## Socioeconomic, Race, and Ethnic Differences in Health Status

- Investigations should identify the social, genetic, and biologic determinants of differences in health status among women of different socioeconomic, racial, and ethnic groups.
- Studies should determine the full spectrum of determinants of disability and injury in women of various socioeconomic, racial, and ethnic groups.

Any research initiative directed at any of the questions listed above should include, when feasible and appropriate, low-socioeconomic and minority women in sufficient numbers to answer the research questions concerning these groups.

## Other Important Research Areas

The following research questions have a high priority but do not fit neatly into any one of the research themes noted above.

- Studies should identify the lipid parameters in women that indicate a high risk for cardiovascular disease. This work could lead to the formulation of a gender-specific rational strategy for screening heart disease in women, as well as knowledge for formulating optimal treatment and prevention strategies.
- Research should determine the appropriateness and cost-effectiveness of screening strategies that are currently proposed or in practice for women, focusing specifically on cholesterol and bone density screening.

## Special Issues

The NIH should stimulate and encourage creativity within the scientific community in developing and executing the studies needed to fill the research gaps noted here. One mechanism for doing so is to issue program announcements soliciting the development of studies in targeted subject areas. Thus, investigators will be given the opportunity to develop ideas on the cutting edge, to have these ideas peer-reviewed, to improve them appropriately, and eventually to receive funding. This funding mechanism, rather than Institute-directed research via Request for Proposals, is in the best interest of women's health. In another possible mechanism, funds would be set aside specifically for women's health research.

Experts in women's health issues and sufficient representation of women scientists should be included on standing NIH study sections and ad hoc review committees. Universities and other grantee institutions should be encouraged to promote the number of women who are principal investigators on research grants. Finally, funding should be ensured to support important new initiatives as outlined in this and other working group reports.

The manner in which the women's health research agenda is implemented is just as important as the particular research questions that constitute this agenda.

## **MATURE YEARS**

*Cochairs:*  
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**T**oday, women constitute approximately 59 percent of the U.S. population age 65 and older. Among people age 85 and older—a group whose overall size is expected to double during the next few decades—women make up nearly three-fourths of the population. Therefore, it is important to illuminate the nature of the burden borne by women age 65 and older in terms of the health problems that afflict them, especially chronic disease and disability. This will be crucial to improving the health of all Americans and, at the same time, attaining a significant reduction in total health care costs.

Women as a group share a biological and psychological sturdiness that has afforded them a distinct survival advantage such that, throughout the industrialized world, there is a mortality gender gap of 4 to 10 years during the later years of life. Females are also somewhat less likely to succumb to the violent death or lung disease<sup>1</sup> that overtakes many males in their first half of life.

Women survive through the decades that claim their male counterparts with cardiovascular disease and cancer, providing care and succor; however, when women develop these diseases, they

may no longer have available social supports or caregivers for themselves. In addition, if women survive the common diseases, they often live long enough to develop the devastating illnesses that are unique to the very old: peripheral vascular diseases, geriatric malignancies, the musculoskeletal arthritides responsible for pain and immobility, and neurological degenerative diseases such as dementia and movement disorders.

Besides the possible loss of family and other social supports, there are other psychosocial burdens with which women must cope during the years past age 65. These include transitions between roles (from wife to widow, for instance), the psychological impact of devastating illness, loss of work-related self-esteem after retirement, and loss of esteem resulting from the onset of frailty and dependency.

Health statistics show that women's incidence rates of acute conditions (diseases that last no longer than 3 months) over their life span is 20 to 30 percent greater than are men's. In all of the principal categories of acute conditions, an excess occurs among females, including infective/parasitic diseases, respiratory conditions, digestive system conditions,

and injuries. Furthermore, after age 65, women experience an excess of chronic conditions as compared with men in the same age group.<sup>2</sup> Chronic conditions are long-term health problems—both diseases and structural or sensory impairments. Women's excess prevalence is particularly high for several musculoskeletal conditions, most digestive disorders, and thyroid diseases. Prevalence rates for osteoporosis, per 100 women, were relatively low for those ages 45-49: 17.9; but for all subsequent age groups, incidence rates rise rapidly: 39.2 for those ages 50-54; 57.7 for women ages 55-59; 65.6 for females ages 60-64; and 73.5 among those ages 65-69. For women age 75 and over, the rate was 89.0.<sup>3</sup>

Based on prevalence rates per 1,000 persons that are expressed as sex ratios (female/male), recent data serve to illustrate the excess burden of chronic conditions borne by women. Women ages 65-74 more frequently had: spastic colon (sex ratio, female to male, 6.24); thyroid diseases (ratio, 5.16); chronic enteritis and colitis (ratio, 2.62); and arthritis (ratio, 1.43) than men of the same age group. However, among the survivors that constitute the group age 75 and over, female/male ratios for some conditions more closely approach parity: for example, for spastic colon, this ratio is 2.25; for thyroid diseases, 3.43.

Further, there is a body of clinical geriatric literature reporting unusual presentations of disease. These can cause diagnostic dilemmas, and they also serve to illustrate some of the gender-related differences that can occur in onset, pathophysiology, response to treatments, and outcomes. However, there has been minimal research on either the gender-salient or gender-specific biological and psychological (developmental) processes that lead to disease and frailty in older women. This literature could serve to generate many testable hypotheses.

Other conditions that do not of themselves have a severe impact on physical health may have a major impact on women's ability to function and participate in life. For example, there are more than 2 million community-dwelling adults in the United States who experience urinary incontinence; twice as many women as men are at risk. Approximately 50 percent of all residents of nursing homes are incontinent.

***"When you look at the overall statistics—[for example] women on average live 7 years longer than men—that raises significant implications for long-term care and coping with chronic illness."***

*Joan Kuriansky, The Older Women's League*

Some diseases that afflict women may involve gender differences in brain dysfunction. However, some of the gender-related differences in their incidence may simply reflect an increase in survival of women versus men. These include sleep disorders<sup>4,5</sup> and neurological degenerative diseases such as dementia, certain psychiatric disorders, and movement disorders—notably, tardive dyskinesia (which occurs more frequently in older women and increases further with any type of brain damage) and a higher rate of drug-induced parkinsonism. Sleep disorders in particular are more common in elderly women, including longer sleep latency and early morning wakening. Sleep apnea with hypoxia may be underdiagnosed in women, especially if they are widowed and sleep alone.

Epidemiologic studies have shown that there is an increasing incidence of dementia with age—particularly senile dementia of the Alzheimer's type—in older women. Over age 70, the prevalence of dementia doubles every 5 years. These primary neuronal degenerative diseases may be more complex in etiology than is currently understood and may represent gender-specific, rather than gender-salient, disease processes.<sup>6,7,8</sup> Alzheimer's disease may be associated with familial risk, increased paternal age, a family history of Parkinson's disease, and the frequency of earlier thyroid disease (especially in women).

Mental health problems afflict women over 65 years to a greater degree than men in the same age group. Several are more prevalent and serious in women, such as depression, anxiety spectrum disorders, mania, and late-onset psychosis, especially of the paranoid type, which appears to have a 6:1 female-to-male sex ratio.<sup>9</sup> Depression

in elderly women has a prevalence of 3.64 percent, versus 1 percent in elderly men. Research needs to address the problem of anxiety in elderly women. In general, it is two to three times more common in women than men and includes panic disorders, phobias, and generalized anxiety disorder. However, social anxiety disorder and obsessive/compulsive disorder are only slightly more common in women. Not enough is known about anxiety spectrum disorders in elderly women; panic disorder may wane while phobias persist. It is known that earlier in life, mania is more prevalent in males. However, beyond age 60, prevalence switches, and mania occurs more frequently in females.

The excess in incidence rates for women of acute, chronic, and mental health conditions, along with any concomitant psychosocial issues, translates into significant problems for women in coping with the demands of daily life. Data from the 1990 National Health Information Survey (NHIS),<sup>1</sup> for example, show that among women ages 65-74, approximately one in five is either unable to carry on a major activity of daily living or limited in the amount or kind of activity she is able to perform. These data show that women currently residing in nursing homes outnumber men by nearly three to one.

## **Major Themes**

As recommended in the recent report by the Institute of Medicine Committee for a National Research Agenda on Aging, *Extending Life, Enhancing Life*,<sup>9</sup> research is needed to address the gender-related molecular and cellular physiological processes important to the last decades of life and to gain an understanding of how these biological changes influence the behavior and well-being of older women. The challenge is to explore how the developmental processes in basic biology across the life span of the female interact with psychosocial factors and aging such that wellness is maintained in some of the elderly, whereas illness burdens others.

These developmental processes include alterations in gonadal function that accompany menopause and changes in pituitary and hypothalamic homeostasis, as well as senescent immune and

neuroendocrine function in women over age 65. One goal of this research is to make the duration of time spent in the frail state as brief as possible before death. These issues are important because it is the frailty and accumulated illnesses of the elderly that not only strain the health system—both acutely and chronically—but also deprive the old of dignity and quality of life in their last years.

In addition, women in their mature years experience significant psychological and social changes across the life span. These include losses of many types (e.g., death of loved ones), maladaptive illness and health behaviors, and transitions between roles (natural versus unnatural sequences—for example, the death of children or having to function as parents for one's own parents). Since women are often the major caregivers, they experience these changes most acutely. Potential consequences include increased vulnerability and loss of control over one's body, a decline in self-care, and loss of work-related self-esteem, possibly accelerating the onset of frailty and dependency.

The impact these changes have on survival is most pronounced for women of lower socioeconomic status (SES). This fact gives rise to many cultural- and ethnic-relevant questions. Do the issues raised reflect economic, social, or ethnic health habits, or some interplay among these factors? What are the specific barriers to access and utilization of health care? What are the psychological as well as biological implications of care-giving for and by the mature female? How does potential institutionalization and fear of dependency impinge on women's health? How can the increased prevalence of depression be prevented or reversed? How are the ethical issues of providing or withholding care to be confronted in light of the recognition that the latter decision is essentially equivalent to rationing of care?

To provide a framework for the individual studies that investigate the causes and consequences of disease and disability in older women, the mechanisms—genetic, neuropsychiatric, psychosocial, immune, and hormonal—that differentiate men and women, and how these affect health and longevity, need to be determined. Studies are needed to explore, for example, these differences between

men and women in relation to factors such as body size and composition, pharmacokinetics and pharmacodynamics of drug metabolism, nutrition, and brain asymmetries in cerebral blood flow and lateralization patterns. Research should encompass studies of anatomic gender differences in relation to right- and left-handedness, using neuropsychological testing and brain imaging techniques. Although most studies have not analyzed data based (at least in part) on gender differences, one or two such studies do exist. And, as with neuropsychological testing, data need to be generated, or collected from existing studies, for the “young-old” and “old-old.” Brain imaging is evolving for neuropsychiatric applications, but gender differences need to be explored further.

Other important research areas, which will require contributions from molecular and cell biology, include studies of gender-related differences in growth factors, including neurotrophic factors. There is also a need to determine the specific interrelationships between environmental and genetic host factors that result in conditions such as the dementia diseases. High-priority longitudinal studies should include those focused on evaluating the relationship of age-related memory loss to dementias such as Alzheimer’s disease.

In addition, the particular biological and psychosocial mechanisms that result in women’s vulnerability to specific diseases and to frailty need to be determined. Examples may be found in studies of the frail elderly that might provide a window for identifying the risks that can then be addressed in research on prevention and health maintenance. Biomedical research should determine the factors that modify the impact of these biological and psychosocial mechanisms in subgroups of women defined by race, SES, health-related behaviors, occupation, reproductive history, and dietary patterns.

## **Key Issues/Research Recommendations**

### **Research on the Long-Term Effects of Menopause (in Elderly Women)**

- Major longitudinal studies should determine the full range of interactions between the biological processes of menopause and concomitant behavioral and social factors, to assess how

these affect the health and functioning of women during their older years. In order to differentiate the effects of menopause from those of aging and compare changes in women with those in men of comparable age, bodily changes need to be monitored in bone, the cardiovascular system, metabolism, hormones, immune function, collagen, strength, fitness, body composition, and psychological and sociological variables.

***“There is little information on the natural course of the endocrine system and tissue changes occurring during menopause. We know very little about the wide variations in symptoms during the menopausal years—why some women notice relatively few symptoms and others experience degrees of dysfunction.”***

*Patty Looker, Executive Director,  
The National Association of  
Women’s Health Professionals*

- Studies should establish the normal range of physical and mental health changes that accompany menopause and also identify the signs and symptoms of an abnormal menopausal course. With this information, clinicians will be able to identify those women who could benefit from various kinds of therapy during menopause. In particular, little is known about the ways in which women are affected by menopause in the social and behavioral context.
- Research must clarify how the changes that occur at menopause affect the body at the molecular biological level, as well as on how these actions may have influenced the overall health of older women. For example, it is not known what happens when bone cells are deprived of estrogen.

- Research should investigate whether these changes at the cellular level can be altered by factors such as exercise.
- Research is necessary to learn the mechanism by which important physiological variables such as low-density lipoprotein level change after menopause.
- Studies should examine how changes in estrogen levels after menopause might alter the clinical response to drugs and other kinds of therapies commonly used in older women.

## **Substance Abuse**

- The most common patterns of substance abuse (and the range of variation) among women over the life span need to be determined. These patterns should be compared with those obtained for men for any significant differences.
- Factors that lead to substance abuse versus avoidance over a woman's entire life span should be determined.
- Differences in rates of alcohol and drug metabolism consequent to aging in women, and how these affect the use and abuse of alcohol and drugs, should be measured.
- Studies should determine the precise relationships between the use of alcohol, tobacco, prescription and over-the-counter medications, and illegal substances in socialization and the development of disability, dementia, and psychosocial problems.

## **Disability**

- New, large-scale epidemiological studies should be conducted to provide a comprehensive picture of the prevalence and severity of disability in older women; comparative data on men of similar ages will be highly useful as well.
- Cross-sectional studies should identify the current disability status of elderly women in different geographic areas (rural versus urban); of various racial and ethnic groups; in differing living arrangements; and of differing socioeconomic, marital, and occupational status.

- Longitudinal studies are also important to evaluate the factors responsible for the development of functional disability in the above-mentioned groups.
- Research should investigate the consequences of functional disability that are unique to the older woman. More specifically, investigations should determine the effects of functional disability on health care utilization, health perceptions, SES, and quality of life. For example, functional disability in one domain may cause a woman to label herself as old or ill.
- Studies should explore how self-perceptions might mediate the search for appropriate health care or willingness to follow recommended health practices.
- The possible role of interventions such as physical activity in enhancing a broad variety of functions needs to be explored. Sufficient preliminary data have been collected to justify a more intensive effort to define the types, intensities, durations, and frequencies of physical activity needed to produce a significant effect on muscle strength, endurance, bone density, serum lipids, glucose tolerance, cardiovascular and pulmonary function, atherogenesis, and psychological health and well-being.
- Studies should clarify the influence of secular trends (e.g., addictive behavior, exercise, and diet) on the risk for disability in the various racial, ethnic, and SES groups.

## **Preventive Health Behaviors**

- Research should discern why older women, as compared with younger women, have lower rates of preventive health behaviors for breast cancer and other conditions to which they are particularly vulnerable. For example, the role of socioeconomic factors, health perceptions, social supports, attitudes toward aging, and current medical practices should be investigated.
- Studies should determine which behavioral or social interventions are effective in motivating older women to make greater use of preventive health services.

- Investigations are necessary to learn how to motivate health care practitioners to make greater use of preventive strategies in older women.

## Social, Cultural, and Psychological Issues

It is important to determine the ways that cultural and social environment perceptions of, and attitudes toward, older women influence their health and quality of life.

Clinical impressions suggest that stereotypes concerning unattractiveness, asexuality, and decreased utility to society can result in infantilization of older women by health care providers, who may be less willing to spend time with their elderly female patients. When providers exhibit paternalistic behavior, they minimize the patient's sense of control.

- Research should identify the prevalence of various forms of age stereotyping and their application to specific target groups; this information is highly relevant to successful interventions and delivery of care.
- Studies should analyze the ways that older women influence their own health and quality of life. Negative self-perceptions can adversely affect self-care and assertiveness in obtaining health care, as well as increase social isolation and dependency. Possible examples for potential research areas include negative body image, lowered self-esteem, and perceived loss of control.
- Studies should explore how these self-perceptions might mediate the search for appropriate health care or willingness to follow recommended health practices.
- Psychological factors and personality variables that mitigate the impact of health- and non-health-related stressors in older women should be explored. Certain individual characteristics may serve to buffer the elderly from the effects of stressors and thus enhance adaptation.

- Studies should analyze perceptions of control and meaning, attentional and attributional factors, and problem- and emotion-focused coping among older women.

## Use of the Health Care System

Diverse factors—practical, psychological, cultural, and educational as well as those pertaining to the U.S. health care system—may play a role in restricting access to, and utilization of, health care by older women. Many barriers have been identified, but we know little about the relative impact or differential impact of these hindrances on various racial and ethnic groups.

Practical barriers to health care in older women include poverty, cost, transportation, family responsibilities, and physical accessibility. Medical system barriers include physician and staff attitudes; reimbursement policies that effectively curtail patient contact time and diagnostic and treatment options; inadequate knowledge of geriatrics by health care providers; omission of appropriate diagnostic examinations and procedures such as routine pelvic, rectal, and breast exams; and exclusion from consideration for invasive treatment modalities such as coronary artery bypass grafting, carotid endarterectomy, and surgical correction for incontinence and prolapse.

Psychological barriers to health care in older women include denial of illness, fear of institutionalization, perceived significance of symptoms, and fear of negative labeling (e.g., as senile or incompetent). Cultural and educational barriers to health care in older women include changing disease models, belief in different modes of healing, and lack of knowledge about—and familiarity with—the health care system. A variety of influences may affect an elderly woman's decision to initiate, sustain, or resume self-care, screening, and treatment regimens.

- Research should determine which factors play a role in determining health care behaviors. These factors may include education, race, social support networks, cognitive functioning, motivation, psychological status, and a sense of effectiveness in managing one's own life. The nature of the health care behaviors themselves may also play a role.

## Evolving Roles and Lifestyles

Evolving roles and lifestyle changes, especially those that involve high-risk behaviors and lifestyles, can affect the health of older women. These sources of heterogeneity require cohort-specific research designs, so that the influence of each particular cultural context can be determined.

It is important to understand the determinants of effective functioning and quality of life in older women and, conversely, to learn which factors place limitations on the functioning and quality of life in the frail elderly.

- Research should explore the impact of substance abuse, divorce, occupation, fertility patterns and contraceptive use, and multiple role transitions (e.g., having to serve as a parent to one's own parents and adult children).
- Studies should explore the consequences of the chronic illness burden, perceived and real functional dependency, locus of control, visual and auditory impairments, urinary incontinence, social interactions, and psychological status.
- Valid and reliable measurement tools are needed for assessment of quality of life. These are currently lacking and should be a priority.

## Special Issues

### Methodology

The Medicare data base provides a unique opportunity to study very large samples of individuals at relatively low cost. Nonetheless, the data bases in current use are inadequate, unless performing relatively crude analyses.

- The NIH should work with the Agency for Health Care Policy and Research (AHCPR) to better utilize the Medicare data base. Specific studies should be conducted on the unique populations of women that can be identified through this large data base, such as the elderly population in general, older minority populations, rural versus urban individuals, and those with less and more education. These studies could focus on the development of disability as well as on specific diseases.
- The AHCPR, in collaboration with NIH, should begin to consider the collection of specific data on samples of both men and women that can be utilized in subsequent longitudinal evaluations of disability, functional changes, and risk factors for disease.
- New methodologies should be developed to address the specific health-related research issues of older women.
- Studies should analyze gender-specific problems in sampling, recruitment, and retention in clinical studies and analysis of data.
- Because of the heterogeneous nature of the population of older women, methods of data analysis that both permit the simultaneous study of multiple variables and take account of overlapping distributions are needed.
- To attain a better measure of disability among women, the state of the art in assessment of functional state should be documented.
- Research should determine how best to evaluate the efficacy of traditional "geriatric interventions" and address questions such as whether geriatric management differs from good medical practice, which emphasizes an understanding of the pathophysiology of the diseases and behaviors of the aged.
- Researchers should develop new methods of measurement that use age-relevant samples in regard to gender differences in a variety of biological functions, or adapt current methods.

## Cost of Laboratory Tests

A major limitation to successful research on older individuals is the high cost of laboratory tests. Many of these tests are paid for by Medicare and other third-party providers when used primarily in clinical care. The costs of these tests, such as magnetic resonance imaging, ultrasound, echocardiography, bone scans, and many complex laboratory assays, however, are not reimbursed when they are used in research protocols. Such costs substantially drain available research funds, especially those for research on aging, and therefore reduce the amount of funds available for important research projects or limit their scope.

It would be far more logical to develop a relationship with AHCPR and other insurers of these older cohorts that would make it possible to pay for these research tests as a component of clinical care. The extra cost to insurers such as Medicare would be minimal and within the budgets for clinical care; in actuality, the cost could be easily recouped by decreasing, by a very small amount, the overall payment for the clinical tests.

- The NIH should proceed, with AHCPR, to develop a plan to cover more equitably the costs of complex testing within research protocols funded by NIH. Such an approach may reduce the overall cost of research and, at the same time, improve clinical care for a large segment of the U.S. population.

## Inclusion of Women in Studies

There are some unique ethical issues that need to be addressed with respect to research on older women. In particular, the exclusion of older women from disease-specific longitudinal studies and from drug and treatment protocols needs to be re-evaluated. In current medical practice, treatment strategies are not developed explicitly for mature women, but are instead extrapolated based on data from trials on males and/or (more rarely) on younger or middle-aged females.

- Studies should determine how to expand current coronary risk studies as well as postinfarct, coronary artery bypass grafts and clot lysis, angioplasty, and cancer chemotherapy trials in older female populations.

It is important to determine whether the reasons offered for excluding older women from their participation in research, such as psychological or physical frailty, are, in fact, justifiable. Perhaps these rationales serve merely to exclude women unfairly from the benefits of research. Limiting participation of older women in research may result in *de facto* rationing of health care. This practice may have implications for health care policy.

In summary, research into the preservation of health and quality of life for older women and into the reduction of frailty across their life span, especially at its end, requires the expertise of many scientific disciplines. This provides a remarkable opportunity for cross-Institute support for longitudinal and cohort studies of normative functions as well as of disease development. Future research pertaining to older individuals should utilize study cohorts as much as possible, include the evaluation of multiple end points, and facilitate crossover among NIH institutional research areas. The opportunity to utilize existing large and available populations, especially of older individuals, for testing new hypotheses should be carefully considered. Reducing the institutional barriers to coordinated research within NIH should be a high priority.

Studies on the population of the women over age 65 telescope the broad spectrum of issues that pertain to studies on the “burdens” of survival and can provide special insights into the complex processes that modulate health in women of all ages. This may be a particularly opportune time for a trans-NIH Coordinating Committee to focus on and improve the health of older women as its first priority.

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## REPRODUCTIVE BIOLOGY

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**O**f all bodily functions, reproduction is one of the least understood. This is due, in part, to the awesome complexity of the systems that govern all aspects of the reproductive process and to major differences among species in the nature of these control systems. These differences can cause confusion when results obtained in animal models are inappropriately extrapolated. Ethical prohibitions and other considerations can also impede the study of reproductive processes in normal women.

### **Major Themes**

Striving to understand procreation in humans is itself a sufficient rationale for research in this difficult area, but it also is true that most disturbances in the reproductive health of women can only be prevented and treated if the basic physiology of the reproductive system is understood. In addition, research can shed light on the possible hindrances to interrupting fertility: this information is essential for developing new means to promote or prevent fertility, both critical health issues for women. In the future, as in the past, astute and knowledge-

able clinical investigators must apply their experience across a wide range of biological disciplines to achieve progress in this quest for knowledge.

There are many issues that influence the reproductive health of women. Several of these that require intensive exploration have been selected for discussion here, because so little is known about them and because they have profound clinical importance.

### **Key Issues/Research Recommendations**

#### **The Brain, Pituitary Axis, and Reproductive Function**

Follicular development, ovulation, corpus luteum formation, and the initiation of pregnancy depend on the proper functioning of the neuronal system, located in the hypothalamus, that causes the rhythmic release of the neuropeptide gonadotropin-releasing hormone (GnRH) into the pituitary portal circulation. This release, in turn, occasions the pulsatile release of the gonadotropic hor-

mones that control all aspects of ovarian function. The nature of this GnRH “pulse generator,” a neurophysiological entity that is central to all reproductive processes, is essentially unknown. It is necessary to learn its cellular basis, the role of GnRH cells, and how these cells are integrated to produce a coordinated discharge. In addition, it is not yet known how ovarian steroids, prolactin, opioids, and other neurotransmitters modify the frequency of GnRH secretion and how they are transmitted to the GnRH pulse generator via environmental cues. Additional data are required to understand the link between energy metabolism and reproduction, the relationship of the hypothalamic pituitary adrenal axis to the reproductive axis, the effect of disruption of circadian patterns on the pulse generator and how is it mediated, and how depression affects physiology at this level. The mechanism that governs quiescence of this pulse generator during childhood and its awakening at puberty needs to be determined. And further study of the changes that occur at the level at which GnRH is secreted in women during menopause and the perimenopausal years is needed.

It is known that more than 80 percent of women with ovulatory dysfunction have associated abnormalities of pulsatile GnRH secretion. It has been demonstrated that pulsatile secretion levels of GnRH drop in hypothalamic amenorrhea with increased exercise, caloric deprivation, stress, hyperprolactinemia, and unknown causes. Furthermore, abnormal activity of the hypothalamic pituitary axis is likely to feature prominently in the etiology of polycystic ovary syndrome (PCOS). These two conditions, hypothalamic amenorrhea and PCOS, account for 50 percent of all infertility resulting from internal factors and also for the failure of many women to accrue normal bone mass. These conditions thereby pose a significant risk for osteoporosis and its sequelae. Dysfunctional uterine bleeding is another possible consequence in women who do not ovulate regularly, with its associated increased risk of endometrial cancer.

The mechanism of GnRH that acts on the gonadotrophs of the pituitary gland is not understood completely, nor are the cellular mechanisms responsible for the profound changes in frequency

of the GnRH pulse generator on gonadotropin hormone secretion. There is compelling reason to believe that in women, as in female primates, the preovulatory gonadotropin surge is initiated by a positive feedback of estradiol on the pituitary gland. How this steroid can both inhibit and stimulate gonadotropin secretion at the level of the gonadotrophs is completely unknown. While GnRH can stimulate both luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion, the latter appears to be controlled independently in a variety of circumstances. How the differential secretion of FSH and LH is achieved, and the role of endocrine, paracrine, and autocrine factors in this phenomenon, remain to be fully delineated, and their mechanisms have not yet been determined.

The cellular mechanisms that change the frequency of GnRH input to alter the relative secretion of the FSH and LH need to be clarified, as do the relative roles of other endocrine, autocrine, and paracrine factors in this differential. The ratio of FSH and LH secreted by the pituitary has an important influence on ovarian follicular growth and differentiation as well as on steroidogenesis at the ovarian level. A relative increase in FSH secretion is critical for normal folliculogenesis. A persistently abnormal ratio of LH to FSH can inhibit the normal production of androgenic steroids by the ovary, as observed in PCOS, and may also be responsible for the failure to select a dominant follicle, which likewise occurs in this disorder.

It is important to learn how the hypothalamus/pituitary changes from a system that responds to inhibitory control by sex steroids to one in which positive feedback causes a key event of the cycle, the LH surge, on which ovulation depends. The relative contributions of the hypothalamus and pituitary appear to differ among species. In this area, particular attention needs to be paid to the use of appropriate animal models.

- Studies should identify and investigate the cellular basis of the GnRH pulse generator using cell lines, neuroanatomic studies with computer modeling, electrophysiologic studies, and clinical investigations. Studies should emphasize the ways in which GnRH-secreting neurons get to

the hypothalamus from their origin in the olfactory placode; the ways in which environmental cues (nutrition, exercise, light/dark cycles) are processed and may impinge on the pulse generator; and the development of tools to probe the neuroendocrine axis in the human, including neurotransmitter modulators and detailed experiments of nature (e.g., GnRH deficiency-ablation/replacement models).

- Research should address the differential secretion of LH and FSH from the pituitary by investigating the mechanism by which GnRH pulse frequency affects synthesis and secretion of the gonadotropins; the mechanism by which steroids, inhibin, activin, and other peptides act at the pituitary in physiologic and pathophysiologic processes; the factors (hypothalamic and pituitary) responsible for the midcycle surge; and the cellular mechanism of positive feedback.
- Studies should investigate the developmental control of GnRH secretion, focusing on factors that control the quiescence of the GnRH pulse generator in childhood and the pubertal transition; longitudinal studies of girls across puberty, investigating steroid, gonadotropin, and ultrasound changes in different ethnic groups, possibly identifying subgroups at high risk for pathophysiology (e.g., PCOS and hypothalamic amenorrhea); and longitudinal studies of the perimenopausal transition, including studies of natural history, of ideal markers identifying risk factors for adverse outcomes of the menopause, and of the genesis and control of hot flashes.
- Studies should determine optimal therapeutic interventions based on pathophysiology in order to improve and develop alternative methods of contraception, with additional attention paid to compliance and acceptability; improve treatment of infertility resulting from ovulatory dysfunction, optimizing ovulatory rates and decreasing risks of multiple gestation and ovarian hyperstimulation; maintain regular cycles (steroid replacement may be inadequate and/or undesirable in young women with hypothalamic amenorrhea); determine the appropriate time and best methods for intervention during the perimenopause; and control hot flashes.

## Ovarian Functions and Their Control

The ovary, like its homologue the testis in males, serves two principal functions. As a reproductive organ, the ovary is responsible for the production of the female gametes (oocytes). As an endocrine organ, the ovary produces the female sex steroids which, in addition to their essential roles in the reproductive process, also serve to maintain homeostasis in calcium and lipid metabolism. Disturbances in ovarian function, therefore, affect not only the reproductive capacity of the individual, but may also jeopardize general health.

The functional unit of the ovary is the follicle. Composed of a variety of cell types, the ovary is responsible for housing dormant oocytes, and initiating and sustaining the maturation of oocytes for ovulation as well as producing the sex steroid hormones. After the release of the oocyte at ovulation, the follicle undergoes structural and functional changes that result in the formation of the corpus luteum, which produces progesterone, a hormone that is essential for the maintenance of pregnancy. Of the 2 million follicles that are present at birth, only about 500 will ever ovulate; the other 99+ percent will undergo atresia throughout premenopausal life. To understand the mechanisms responsible for normal follicle development as well as those involved in follicle atresia, thorough knowledge of these processes is required.

The factors and mechanisms that govern the initial formation of primordial follicles within the embryo are unknown. Nor is it known what regulates the maturation and atresia of these follicles, some of which may lie “dormant” within the ovary for as long as 45 years before their maturation commences. Unlike the more advanced stages of follicle growth, the initial growth of primordial follicles does not appear to require the pituitary gonadotropic hormones. When more is known about these processes, it may be possible to understand premature ovarian failure (premature menopause), in which the supply of follicles is exhausted well before the expected time of menopause. In addition, understanding the mechanisms that stimulate the maturation of primordial follicles may help in designing more effective methods for both restoration of fertility (stimulating primordial follicular growth) and contraception (inhibiting primordial follicular growth).

The reasons why most follicles undergo atresia, and only a few actually mature to the point where they release an oocyte, are largely unknown.

Although it is known that the pituitary gonadotropic hormones FSH and LH are required for this process, it is not known why only one follicle actually matures each month. Within the past decade, substantial progress has been made in defining the individual roles of FSH and LH on follicle growth, information that has been of benefit to practicing clinicians in the hormonal treatment of some forms of infertility. However, researchers still need to learn how the gonadotropic hormones interact with locally produced autocrine or paracrine growth factors and how this process may contribute to the selection of a single follicle. Many women are anovulatory despite the fact that their ovaries contain immature follicles, and it has been proposed that there may be subtle differences in the expression of growth factors within their ovaries. Further, understanding the relationships between the gonadotropic hormones and growth factors such as the insulin-like growth factors (IGFs) may help explain the cause of PCOS, which is associated with anovulation, hypoestrogenism, and masculinization.

The factors responsible for the development of the oocyte are little understood. Specifically, neither the stimulus nor the mechanisms that initiate meiosis, which is responsible for the production of the haploid gametes, are known. The structural and chemical features of the mature human oocyte that enable it to be fertilized by a spermatozoon need to be clarified, as does the extent that disorders of oocyte maturation contribute to "unexplained" infertility. Although there has been substantial study of the biology of human sperm, very little is known about human oocytes. Obviously, such knowledge would contribute greatly to our understanding of fertility and infertility and may also help in identifying new points of vulnerability for novel contraceptive techniques.

Following ovulation, the ruptured follicle is transformed into a corpus luteum. During this transformation, the pattern of hormones produced changes from predominantly estrogen to progesterone. Because progesterone is absolutely required for

the establishment and maintenance of pregnancy, the corpus luteum is essential for the first 4-6 weeks of pregnancy, until the placenta assumes major responsibility for the production of progesterone. Disorders of corpus luteum function with inadequate luteal phases can occur; either the corpus luteum regresses prior to being "rescued" by the implanting blastocyst, or the progesterone secretion is believed to be suboptimal for implantation, which may contribute to infertility as well as to recurrent pregnancy losses. Additional work is required to determine what may cause this premature regression of the corpus luteum or the suboptimal progesterone secretion. Moreover, it must be determined how to measure an inadequate luteal phase (i.e., the lowest progesterone concentration capable of supporting a normal pregnancy), because many women are evaluated for luteal phase disorder in the absence of a true definition of what constitutes a normal and abnormal luteal phase.

A major portion of female reproductive disturbances, such as infertility, male hormone excess, and menstrual dysfunction, are related to ovarian dysfunction. The two major causes of dysfunction are PCOS and ovarian failure (physiologic and premature).

### ***Polycystic Ovary Syndrome***

PCOS is the most common endocrine disorder among women of reproductive age. It is characterized by an excess of male hormone, disordered gonadotropin secretion, and insulin resistance. In most cases, the ovaries have a consistent appearance on ultrasound, with some ovarian enlargement and multiple peripheral follicular cysts. Although more than 50 years have elapsed since its original description, the etiology of this disorder remains unknown. Conservative estimates place the prevalence of PCOS at 6 percent among women of reproductive age. However, a recent study using ultrasonography detected polycystic ovaries in 22 percent of unselected women. Thus, the condition may be much more prevalent than is currently appreciated.

PCOS causes considerable morbidity. The excess levels of male hormone give rise to hirsutism, acne, and alopecia. The gonadotropin secretory disturbances produce anovulation, resulting in

oligomenorrhea or amenorrhea, dysfunctional uterine bleeding, and infertility. If the chronic anovulatory state produced by PCOS is left untreated, it can result in endometrial neoplasia; the mean age of endometrial cancer patients is 32 years.

Fifty to sixty-six percent of PCOS women are obese. Independent of obesity, the majority of PCOS women have profound peripheral insulin resistance. The combination of the insulin resistance and obesity associated with PCOS places these women at high risk for the development of diabetes mellitus. Indeed, 20 percent of obese PCOS women have impaired glucose tolerance, or frank noninsulin-dependent diabetes mellitus, by their 20s. The higher incidence of coronary artery disease may result from the hyperinsulinemia, glucose intolerance, and hyperandrogenism, but the long-term consequences of these conditions have never been investigated.

The most crucial gap missing from current knowledge of PCOS is the lack of understanding the cause(s) of this disorder. Evidence can be found to support a central cause resulting from enhanced LH release, an ovarian/adrenal cause resulting from excessive androgen secretion, or hyperinsulinemia secondary to insulin resistance, leading to PCOS. The close association between PCOS and insulin resistance strongly suggests that insulin (or very similar growth factors) is involved in the pathogenesis of PCOS.

There are several potential drawbacks to controlling ovarian steroidogenesis that are sufficient to require further exploration, such as possible intrinsic abnormalities in steroidogenic enzymes, and/or altered responsiveness to gonadotropin, to insulin, or to other growth factors. It is not known whether the follicular cysts in PCOS constitute a primary lesion or whether they are in fact secondary to the abnormal hormonal environment. The lack of an animal model, preferably a nonhuman primate, has hampered investigative efforts.

The epidemiology of PCOS remains very poorly studied. Preliminary studies suggest that there are major differences in prevalence rates among ethnic groups, with Caribbean Hispanic women experiencing twice the prevalence of PCOS as

white and Black women. Preliminary research suggests that individuals affected by PCOS, and their first-degree relatives (male and female), are likely to have insulin resistance and are therefore at increased risk for diabetes. This relationship should be investigated further. There is evidence that hyperandrogenemia and/or hyperinsulinemia increases cardiovascular risk; this connection needs to be investigated further.

Family studies have indicated a strong inherited tendency for developing PCOS. Nonetheless, the genetics of PCOS and the pattern of its inheritance have not been determined. Genetic studies using linkage studies with candidate genes (e.g., steroidogenic enzymes) and reverse genetic studies to identify the molecular pathogenesis of PCOS are required.

It is clear that PCOS is a heterogeneous disorder. Subphenotypes based on sex hormone profiles, gonadotropin levels, insulin action, adrenal function, and ovarian morphology need to be identified. Optional therapies for PCOS need to be identified for control of male hormone excess, ovulation induction, and insulin resistance. In addition, the effects of weight reduction on reproduction function and insulin sensitivity need to be explored.

- Investigations should analyze the epidemiology of PCOS by racial and ethnic group.
- Studies should determine natural history of PCOS in women over age 40.
- Family studies of PCOS should determine inheritance patterns and to establish kindreds for linkage studies with candidate genes.
- Investigations should explore the effectiveness of hormone replacements and weight loss on cardiovascular function, bone density, and glucose tolerance, as well as their actions at the level of the cell and molecule.

### ***Ovarian Failure***

Physiological ovarian failure occurs at menopause. The complete cessation of menses is preceded by about 10 years of altered reproductive cycles referred to as “the menopausal transition.”

Detailed studies of hormonal changes during this period should be undertaken to determine the impact of different hormonal patterns on bone density and cardiovascular disease risk.

Premature ovarian failure is defined as cessation of ovarian function at age 35 years or younger. This disorder is a common cause of amenorrhea and infertility. Its causes are unknown. Ovarian failure leads to estrogen and other ovarian hormone deficiencies. The consequences of a lack of ovarian hormones include bone loss, vaginal dryness, accelerated atherosclerosis, hot flashes, and mental changes (depression).

The cellular and molecular mechanisms of cessation of ovarian function require clarification. Immune factors may play a role in some cases of premature ovarian failure, which may be associated with other autoimmune diseases and with detectable ovarian antibodies. Deletion of an X chromosome is a well-known cause of ovarian failure, but other genetic lesions need to be explored as well.

The effect of ovarian hormones on the physiology of bone formation and loss is unknown. Risk factors for bone loss and predictors of bone redeposition after therapy, an important issue for the treatment of osteoporosis, need to be identified. Optional hormonal replacement therapy for ovarian failure requires further study to determine the most effective combination of estrogen, progestin, and, possibly, androgen with respect to bone mass, cardiovascular disease, glucose tolerance, mood, and cognition.

- Researchers should identify the determinants of early ovarian follicle formation and development, addressing the initial trigger for the maturation of primordial follicles; the intragonadal factors involved in early follicle growth; and the mechanisms responsible for abnormal follicle growth that lead to premature ovarian failure on hormonal, immunological, and environmental bases.
- Studies should identify the mechanisms by which the pituitary gonadotropic hormones FSH and LH interact with local autocrine and paracrine agents to stimulate the maturation of a single ovulatory follicle each menstrual cycle and determine how these are altered in women who have recurrent ovulatory dysfunction.

- Research should determine the mechanisms by which some genes are stimulated during follicle growth while others are repressed, in a tissue-specific manner, during follicle growth.
- Investigations should determine the factors involved in oocyte maturation and how these may differ in infertile women.
- Studies should clarify the cellular and molecular causes for PCOS and determine whether it is initiated at the molecular level of the hypothalamic-pituitary axis or at the level of the ovary itself.
- Researchers should develop ways to identify this disorder prior to onset of its associated morbidities: oligomenorrhea or amenorrhea, dysfunctional uterine bleeding, acne, hirsutism, endometrial neoplasia, and cardiovascular disease.
- Research should identify the determinants of corpus luteum function and regression and how these contribute to infertility associated with short and inadequate luteal phases.

## Term and Preterm Labor

Preterm birth is one of the major health hazards of humans and the leading cause of neonatal and infant mortality, as well as the principal underlying cause of severe morbidity in infants that survive. The cost of care for an infant in the neonatal intensive care nursery is over \$1,000/day. Many of these infants will have permanent, serious functional deficiencies. The burden of these cases falls heavily on lower socioeconomic groups and women of color. To address this problem, more information about the mechanism that maintains uterine quiescence throughout pregnancy is required, as well as the mechanism that normally induces labor at term when the fetus is mature. It is important to keep in mind that the mechanism of preterm labor may differ from that of normal labor. Preterm labor may represent a fetal response to a noxious intrauterine environment.

Many stimulatory and inhibitory factors that control uterine activity are known. Stimulating factors include estrogen, oxytocin and its receptor,

and endothelin. Inhibitory factors include progesterone, relaxin, and prostaglandins. Other factors, such as steroids, prostaglandins, and relaxin, affect cervical softening and ripening. There are also significant data indicating a calcium-dependent uterine contractile mechanism.

There is a considerable lack of knowledge concerning the physiological interactions among the parts of this complex system. It involves three separate entities: the mother, the fetus, and the placenta and membranes, all of which contribute to the control of uterine activity. It is clear that obstetrical care is effective in reducing the preterm delivery rate; in some populations, such care can reduce this rate from approximately 20 to 8 percent. However, the specific factors in proper obstetrical care that cause the decrease are not well identified.

- Studies should determine the role of nutrition, psychological support, vitamin supplementation, and other factors involved in obstetrical care for their relative effects on prevention of prematurity.
- Research should study the role of stress, substance abuse, race, ethnicity, and maternal age as mechanisms on preterm labor.
- Investigations should focus on the mechanisms according to which drugs, such as tobacco and cocaine, contribute—at the organismic, organ, cellular, and molecular levels—to prematurity.
- Ongoing studies should continue to investigate the value of fetal probes as predictors of preterm delivery.
- Researchers should acquire an understanding of the mechanisms that underlie normal uterine quiescence in pregnancy and its interruption at the end of gestation. This is the ultimate condition for understanding the premature initiation of labor and for preventing it.
- Clinical studies of social, societal, and environmental factors as they affect prematurity are also needed.

Perhaps clinical studies can be designed to isolate the effects of certain risk factors to facilitate their correction. Care providers, such as outreach workers and nurses who have direct contact with patients, may best be able to conduct these studies. However, these providers may need training in study design and the scientific method to assist them in implementing these protocols.

## Hormones and Behavior

The biology of behavior is an area that is still largely unexplored, and only in recent years has it emerged as a focus for research by the various disciplines. The effects of reproductive hormones on behavior need to be addressed in light of provocative evidence indicating that there are relationships between ovarian hormones and affective disorders, cognitive function, and emotional behavior.

During times of rapid hormonal change—such as puberty, the years surrounding menopause, the years that follow it, and the period after giving birth—behaviors alter. Little is known about the physiologic processes or the biology of behavior alterations during these times. A study of hormones and behavior must attempt to determine what is normal for these episodes in a woman's life and how these processes or syndromes should be investigated.

Puberty is commonly associated with moodiness and depression or other negative emotions. After puberty, the incidence of depression is increased four-fold in girls. Negative affect and impulsive behavior increase during this period of rapid hormonal change, particularly during the first two stages of puberty. Researchers need to learn about the biology of these effects—how they relate to hormonal change and how the brain changes at puberty.

Puberty is often a vulnerable time for girls as a consequence of these changes. For adolescent girls, risk-taking behavior is relatively common during puberty; this behavior may be, in part, biologically based. If these changes are due to hormonal events, research should determine whether they are self-limiting and whether they can be controlled or at least better understood. Investigations can address whether Black girls have an ear-

***"Basic research should be aimed at furthering our understanding of the broad range of physiological changes that occur over the entire menstrual cycle. Lack of understanding of this fundamental aspect of female physiology has slowed progress in every aspect of addressing and improving women's health, from breast to ovarian cancer, to premenstrual syndrome, to menopause."***

*Stephanie J. Bird, President,  
Association for Women in Science*

lier puberty and whether behavioral changes occur earlier among these young Black girls.

There is evidence in animals that hormones may affect the brain; learned behavior in the male songbird has shown that the complexity of the song is related to testosterone and affects a specific area in the brain. Evidence also indicates that gonadal hormones exert an effect on spatial ability in boys. Similar studies have not been undertaken in girls. How reproductive hormones affect cognitive function at puberty needs to be explored in girls. Differences among the sexes in mathematical and verbal ability may be influenced by hormonal effects on the brain. Gender differences in socialization also need to be examined.

The perimenopausal and postmenopausal states are associated with rapid estrogen withdrawal. Affective disorders, particularly depression, increase at this time. It is important to study the biological events that cause these problems and discover whether there are any identifiable changes in brain and neurotransmitter function. Studies also need to address how hormone replacement affects the behavioral changes at menopause. The postpartum state has been associated with documented depression and severe psychopathology, yet little is known concerning the degree to which hormones may be contributing to this syndrome.

Also, the problems of depression and behavioral changes in the premenopausal and postmenopausal periods and postpartum need to be defined from a biologic perspective. For instance, the effects of estrogen intervention in a randomized study could serve as a means to further define the effects of estrogen withdrawal on affective behavior. Or a study could be designed to quantitatively assess possible correlations between severity of depression and estrogen level.

The normal menstrual cycle may include mood and behavior changes and premenstrual syndrome (PMS). This problem may affect up to 15 percent of women, although the severity of the problem varies widely. The biology of the physiologic events that occur in PMS needs to be studied. It is not known whether the changing estrogen/progesterone ratio during the premenstrual interval accounts for these effects or whether they are due to as yet unidentified factors. Eliminating the menstrual cycle completely by the use of GnRH agonists dramatically reduces symptoms, but they cannot be reproduced in their entirety by estrogen or progesterone replacement. It is important to learn whether there are morbid personality states that put women at risk for severe symptoms of PMS and if there are contributing personal or social risk factors. Also unknown are the roles played by stress, nutrition, and aging of the reproductive system in the pathogenesis of the syndrome.

- Behavior in precocious puberty should be investigated, as well as changes that occur with pharmacologic interventions that suppress puberty.
- Studies should use GnRH agonists as a clinical tool, to illuminate the pertinent hormonal contributions.
- Environmental events—such as stress, exercise, nutrition, substance abuse, and the pre-morbid personality—should be studied to determine the contributions of these factors to the syndrome.
- Valid pharmacologic interventions for PMS should be developed.

The development of a normal gender identity in women may be influenced by hormone exposure as early as in the prenatal state. The biology of these events and the ways that gender identity is affected by changes in hormonal events both prenatally and postnatally (e.g., in female children exposed to androgens prenatally and to diethylstilbestrol-exposed daughters) need to be investigated.

Investigations should also attempt to determine the role of prepubertal and postpubertal hormones on gender identity. Experiments of nature, such as exposure of a female fetus to androgens and the problem of gender identity that ensues, should be further defined and utilized as a window for understanding these events.

## **Control of Mammary Gland Growth and Development**

Growth and development of the breast begin at puberty, under the influence of ovarian estrogen and progesterone as well as prolactin. During pregnancy, this growth and development accelerate due to the influence of placental estrogen and progesterone and, most likely, prolactin. Although estrogen and progesterone stimulate breast growth and development, they inhibit the synthesis and secretion of milk. Indeed, milk secretion begins after delivery due to the loss of the placental source of progesterone and estrogen; milk secretion begins automatically even if the baby never suckles. For maintenance of lactation, however, suckling is required because it releases prolactin which, in turn, stimulates milk secretion.

The breast is composed of two cellular elements: the ductal system and the alveoli. The alveoli are the secretory elements. Both the ductal system and the alveoli are stimulated to grow by estrogen, progesterone, and prolactin.

Recent work on regulating breast growth has been conducted primarily on continuous cell lines (human breast cancer cells) and thus, although these studies are important, they have not dealt with the mammary gland as an intact tissue. The importance of dealing with the gland as a tissue arises from the probable significance of cell-cell interactions regulating growth, development, and

secretion. Recent evidence suggests that growth factors such as epidermal growth factor (EGF) and transforming growth factor alpha (TGF $\alpha$ ) are important for mammary cell growth; indeed, the mechanism of estrogen on breast cells may be effected via the stimulation of the secretion of EGF and TGF $\alpha$ . These growth factors, in turn, act in an autocrine fashion (on the cell that secretes it) or a paracrine fashion (on a neighboring cell). Studies at the tissue, cellular, and molecular levels should focus on the following research issues.

- Studies should determine the mechanisms of estrogen and progesterone action in stimulating ductal and alveolar cell growth.
- Investigations should elucidate the mechanisms of estrogen and progesterone that work to suppress the synthesis and secretion of milk.
- Researchers should investigate the mechanisms of prolactin that stimulate mammary cell growth, as well as the mechanisms of prolactin that stimulate milk synthesis and secretion.

Special attention should be given to autocrine or paracrine mechanisms in the foregoing studies; current evidence indicates that locally produced growth factors may be stimulated by estrogen, progesterone, and prolactin.

## **Uterine Dysfunction**

The uterus plays a key part in the triad of hypothalamic, pituitary (central nervous system), and ovarian function in the reproductive system.

There are several key issues that pertain to normal and aberrant uterine function. The mechanism of implantation and its failure need to be studied, as does the role of endometrial secretory proteins in the control of pregnancy or the menstrual cycle. The biochemical and physiologic characteristics of the endometrium and endometrial implants, as well as the interaction between the endometrium and its stromal cells, have yet to be fully determined. More research is needed on the molecular control of uterine-specific proteins and the role of Fallopian tube-specific proteins (e.g., the day 14 protein described in monkeys after fertilization).

The role of growth factors in endometrial replenishment has not been fully determined, and more must be learned about pathological disorders such as dysfunctional uterine bleeding, luteal phase defects, development of uterine fibroids, adenomyosis, and endometriosis.

### ***Endometriosis***

In women, the most frequently diagnosed uterine dysfunction is endometriosis. This is a ubiquitous disease in women of reproductive age, affecting over 5 million females in the United States yearly and cutting across all ethnic and socioeconomic groups. It is described as the most common diagnosis in gynecology, causing countless women to suffer from pelvic pain, dysmenorrhea, dyspareunia, and infertility. In fact, it has been reported that as many as 25 percent of all women in their 30s and 40s have endometriosis. However, the true incidence of this disease is unknown, because subtle symptoms or occult disease are not easily diagnosed.

The natural history and long-term consequences of endometriosis have not been documented. It was first described as a clinical entity in 1860, and current concepts concerning this condition emerged almost 70 years ago. Minimal progress has been made in understanding the pathophysiology of endometriosis. Little is known about the basic physiology of normal endometrium in humans, or the mechanisms underlying these pathological endometrial implants. In fact, while retrograde menstrual flow into the Fallopian tubes is considered a sufficient explanation for the migration of endometrial cells from the uterus to the tubes, this mechanism fails to explain endometriosis of the lung, which can cause significant morbidity—even mortality, if a lung collapses suddenly—as well as endometriosis of the brain, nose, and bone, to cite just a few of the extrapelvic sites where endometriosis has been found in women. It is also not known why all women do not develop this disease; retrograde flow is common—it may occur in well over 90 percent of all cycling women—yet some women's bodies are able to reject this aberrant tissue flowing within the pelvis. Therefore, there may be an immunologic basis explaining resistance to implantation. Alternatively, a global

immune defect may account for implantation, both locally and distally within a woman's body. Pelvic and systemic immunological abnormalities have been implicated in the process of the disease, and it may be etiologic with regard to adhesion formation and infertility.

The most significant consequence of endometriosis is pelvic pain, but urinary and gastrointestinal symptoms and pain with intercourse or exercise are also common. Nevertheless, no clear relationship between the presence of lesions in the pelvis,

***"Endometriosis affects . . . women from all races and socioeconomic groups in the United States. It is a nightmare of misinformation, myths, taboos, lack of diagnosis, and problematic hit-and-miss treatment . . ."***

*Mary Lou Ballweg, President,  
Endometriosis Association*

bladder, or bowel and symptoms exists, nor do these serve as indicators of clinical expression of the disease.

In attempts to cure the disease, over 1.5 million hysterectomies and bilateral oophorectomies were performed on young women between 1970 and the early 1980s. However, the disease may be reactivated after surgery with estrogen therapy. (There are documented cases of endometriosis in men who receive estrogen for prostate cancer; whether estrogen supports the proliferation of endometrial tissue in the absence of a uterus or ovaries has never been studied.) Yet estrogen replacement therapy is vital to prevent the subsequent bone loss and high risk of osteoporosis that these women face. In fact, the disease appears to be associated with reduced bone mass. Endometrial cells may secrete bone-resorbing factors, such as cytokines. This hypothesis is supported by the finding that endometrium is capable of producing these factors in vitro. Such factors could cause uncoupling of the normally balanced sequence of

bone resorption and formation that occurs in bone remodeling, leading to a deleterious impact on bone accrual. It is known that women build bone into the late 20s and early 30s—yet endometriosis, either directly or indirectly, may be preventing optimal bone accrual. This would significantly compromise peak bone density—a key risk factor for osteoporosis. Endometriosis may serve as a useful model for premenopausal bone loss. Ovarian integrity or function may be impaired due to endometrial lesions, which commonly involve the ovaries, leading to aberrant hormonal secretion or the release of unknown factors, which in turn compromises bone turnover.

The diagnosis of endometriosis is often missed, particularly in teens and minority women. In fact, it is widely—but erroneously—thought that the disease does not occur frequently in Blacks despite consistent symptoms. However, symptoms in Blacks are often attributed to pelvic inflammatory disease (PID); thus, delays in diagnosis are all too common.

According to current guidelines, it is not always possible to link the presence of this disease with symptoms. Mild disease, by surgical classification guidelines, may cause debilitating pain, while severe disease, with extensive scarring, may be painless and only diagnosed during an evaluation for infertility. There appear to be different types of lesions (petechial versus powder burns) involved in endometriosis. Whether these confer differing degrees of expression by virtue of their variable activity is not known.

Whether endometrial cells secrete factors that affect fertility adversely needs to be clarified. Endometriosis is reportably present in over 30 percent of the 3 million women with infertility, yet no direct etiologic mechanisms are understood, with the exception of anatomic tubal occlusion by scarring. Furthermore, it is not clear that therapy improves conception. In the short term, infertility caused by endometriosis results in obvious psychological trauma. And nulliparous women are at greater risk of developing osteoporosis.

Therapeutic management is widely controversial. Women may require multiple surgical procedures

for diagnosis or therapy. Yet a cure is rarely achieved, and severe pain commonly persists. Furthermore, surgical intervention may bring about long-term consequences, including adhesions and a spread of the disease. Additional problems persist, such as how to manage a 20-year-old with recurrent disease who wants to preserve and optimize her reproductive capacity or what to advise a 40-year-old with debilitating pain who does not respond to conservative management yet has a markedly compromised ability to work, to exercise, to have sex, and for whom hysterectomy and oophorectomy would confer a long-term increased risk of osteoporosis.

Major scientific findings are limited, but available data have suggested that immune function may be altered in endometriosis. Abnormal autoimmune phenomena, as well as immunological alterations, have been reported; changes in cellular production of cytokines, and possible secretion of interleukins and tumor necrosis factor from endometrial tissue, support the theory that endometriosis has an effect on immune function. Alternatively, immune dysfunction may be the primary defect that allows these aberrant cells to implant. While immune phenomena appear to occur in the pelvic area, overall systemic abnormalities are also described that are more likely to be linked to alterations of the immune system. The presence of increased complement and antiendometrial antibodies in the serum, and immunoglobulins and immune complexes in the endometrium and implants, adds further evidence to support the theory of an immune mechanism directed against the endometrium. The detection of positive antinuclear antibodies suggestive of abnormal polyclonal B-cell activation and the association of endometriosis with systemic lupus erythematosus further support a more global involvement of the immune system. Other aspects of autoimmune disease are also present, such as a preponderance among females, occurrence within families, tissue damage, and multiorgan involvement.

Research goals should include both a basic component and applied clinical investigation with therapeutic, well-controlled trials. A multidisciplinary approach to endometriosis research, encompass-

ing immunology, epidemiology, and clinical and behavioral research, is suggested.

- Basic studies of the physiology of normal endometrium should determine the underlying pathophysiology of this disorder, addressing why it has variable expression, resulting in different short- and long-term consequences.
- The various roles of medical and/or surgical therapy to control or prevent disease sequelae should be evaluated. There are no long-term follow-up studies reviewing the impact of any mode of therapeutic intervention. Reporting long-term outcomes, as well as the initial results of studies, is essential to furthering understanding of endometriosis.
- Studies should assess the usefulness of new tools, such as magnetic resonance imaging (MRI), for both managing and treating endometriosis; through such means, it is hoped that frequent surgical intervention can be minimized.
- Researchers should learn more about the role of the immune system in the initiation and associated phenomena of endometriosis. Use of appropriate animal models to assess local and systemic occurrence, as well as susceptibility and expression of this disease, is critical. Identification of other suspected factors that may be involved in the expression of the disease—such as stress, hormonal alterations, and dietary factors—should be pursued.
- Exploring the relationship between bone loss and the modulation of bone turnover in women with endometriosis, who are at risk of osteoporosis due to the disease process and/or therapy, is vital.
- Evaluating the extent of bone alterations is critical to establish whether this population is at risk of bone loss well before the advent of menopause.
- Determining the mechanism by which endometriosis causes demineralization would clarify therapeutic modalities.

- Studies should investigate whether estrogen replacement therapy is appropriate for osteoporosis and, in particular, determine the relative risk of bone loss versus disease reactivation. It is important to learn whether therapy can sustain normal bone turnover and avert the disastrous long-term consequences of osteoporosis.

### ***Fibroids***

Fibroids, the common name for uterine myomas (leiomyomata), are benign fibromuscular tumors of the uterus that occur in up to 40 percent of women. They are more common in Black women than in white women. They are responsible for 60 percent of all pelvic laparotomies.

Fibroids are estrogen-responsive and regress after menopause or estrogen withdrawal. They are monoclonal tumors that seem to result from single cytogenetic changes in uterine muscle cells. Some fibroids secrete or produce growth factors and hormones, such as prolactin and erythropoietin. The cause of these changes and the role of these secretory products are unknown.

Fibroids can produce pain or uterine bleeding, and the usual treatment is surgical removal of the tumors or hysterectomy. While medical therapy with GnRH analogues is available, this is only effective as long as treatment is continued. This therapy is complicated by diminished estrogen secretion. The long-term effects of this therapy are uncertain; it is also expensive.

Fibroids have been related to infertility. Yet the precise role of fibroids in infertility is not well defined.

Research needs to determine the life history of fibroids. This can be accomplished safely, since fibroids can now be observed over time and distinguished from ovarian tumors. Eventually, it may be possible to manage even large fibroids without interventional therapy.

- Studies should determine the factors that induce fibroids; any racially based differences in these factors should be studied.

- The relationship of fibroids to infertility should be defined.

## **Special Issues**

The use of nonhuman primate models in studies of the physiology and pathophysiology of the hypothalamus-hypophyseal axis should be encouraged and supported. In addition, the need continues for high-quality clinical investigation in this area.

Addressing and studying ovarian physiology and pathophysiology in humans pose many practical and ethical barriers, the most obvious being the acquisition of ovarian somatic tissues, as well as gametes and preimplantation embryos, for cellular and biochemical analyses. Although subprimate species have played and will continue to play important roles in understanding ovarian function, it is becoming increasingly clear that significant differences exist in ovarian control mechanisms between primate and subprimate species. This is most evident in the local control mechanisms of ovarian function exerted by growth factors, which may play a role in the pathogenesis of ovarian function. It now appears that the intraovarian expression of these factors in rodents differs dramatically from that in subhuman primates. Accordingly, if significant advances are to be made in our understanding of normal and abnormal ovarian function in women, research in appropriate model systems (subhuman primates) must be encouraged and supported.

Currently, appropriate models of human labor have not been used. It has been shown that the fetal adrenal controls labor in sheep, but this

model does not apply to humans. In rodents, the mother seems to control the onset of labor; but this is also a poor model for humans. There is a sizeable body of data to suggest that the decidua may contribute to human uterine contractions by release of prostaglandin, production of oxytocin receptors, and other mechanisms. Developing a higher primate model of human uterine activity would be a useful tool to understanding labor, as would development of good, steroid-responsive human myometrial cell lines.

In addition, animal models need to be developed to examine the effects of hormones on behavior. The use of the primate model should be encouraged, with particular attention to puberty and menopause. In order to understand basic behavior, the full spectrum of action of reproductive hormones should be examined on a complex brain, such as that of the rat. Studies should focus on the neurons involved, the connections between the neurons, the neurotransmitters, and the charges (electropsychological or activation of the genome) of each of the neurons involved and their final output.

Developing an appropriate experimental model for studies of mammary gland growth and development requires special attention. Currently, the mouse mammary gland is the favorite model; its appropriateness needs to be validated using human or other primate tissues.

There is also a strong need for a structure that will encourage interdisciplinary research in many of the areas within reproductive biology, refine reproducible methodology, and facilitate the review process.



## EARLY DEVELOPMENTAL BIOLOGY

*Cochairs:*

*Brigid L.M. Hogan, Ph.D.  
Jerome F. Strauss, M.D., Ph.D.*

The outcome of pregnancy can affect a multitude of a women's health issues over a woman's lifetime. A successful birth improves quality of life not only during the early postpartum period but also during all of the subsequent childbearing years and sets the stage for successful childbearing in the next generation. Complications, such as preterm birth, can be a major compromising factor for a child's growth and development. The consequences of caring for a handicapped newborn infant and child can have devastating effects on health and the quality of life for a mother and for her entire family. Given projections regarding the composition of the American work force by the year 2000, the health of working women during pregnancy and childbearing is of paramount importance to the Nation.

The primary goals of the research initiatives recommended by the working group on Early Developmental Biology are to optimize pregnancy outcome and to understand the basic scientific foundations of normal embryonic development in relation to clinical problems.

The proposed section of the research agenda detailed here has been divided into basic science and clinical priorities. Implementation of both the basic science and clinical programs is essential for an integrated approach to important women's health issues.

### ***Major Themes***

#### ***Model Systems—Methodological Considerations***

Momentous advances in our understanding of human development and growth are occurring, primarily because of technological innovations in molecular biology and genetics, the exploitation of model systems to elucidate basic embryological principles, and the establishment of new methods for studying developmental processes.

Innovations in molecular genetics are leading to spectacular progress in both the identification and cloning of genes affecting the development of the fetus and child. This progress encompasses not only genes for inherited defects such as cystic fibrosis,

muscular dystrophy, and osteogenesis imperfecta but also genes that affect the susceptibility of the child to specific cancers such as retinoblastoma and Wilm's tumor. Research in this area is at the precise juncture between basic molecular genetics and clinical medicine and is fundamentally important because of its prospects for new therapies as well as improved methods for early diagnosis and intervention.

While researchers in molecular genetics have had great success in cloning disease genes, another revolution is underway that affects our understanding of how genes control the shape and form of the fetus. Advances have come primarily from basic research on the development of many different embryos—those of fruit flies, worms, frogs, chickens, and fish, as well as mice. The picture that is emerging indicates that the fundamental processes in the development of all organisms are controlled by a few major families of genes. Some of these genes encode nuclear or DNA-binding proteins that switch other genes on and off and have motifs that are known as the “homeobox,” “zinc finger,” and the “helix-loop-helix.” Other families (the cell cycle genes) encode proteins required for coordinating DNA synthesis and cell division, while yet others (the growth factor-related genes) generate extracellular signaling molecules that allow cells to interact with one another during the formation of complex tissues and organs. Finally, there are families of extracellular matrix proteins—for instance, the collagens and proteoglycans and their receptors—that hold tissues together and help to coordinate growth and morphogenesis in many different ways, for example, by binding growth factors and guiding cell movements. A major area for research concerns the mechanisms responsible for the step-by-step activation of genes that control patterns in model organisms such as *Drosophila* (the fruit fly), the embryo in which many of these genes were first identified.

A common feature of all these families of genes is that specific protein motifs have been highly conserved during evolution. Possibly the most surprising example has been the linear sequence of homeotic genes of insects, each containing the DNA-binding homeobox, which have been con-

served in the same sequence in the mammalian genome and which show a similar axial expression pattern in both fly and mammalian embryos. The power of developmental genetics in flies and worms will continue to offer other insights into human developmental problems. For example, considerable human embryonic wastage occurs because of chromosomal nondisjunction during oogenesis. Although the molecular mechanisms underlying the phenomenon are not yet understood, it has been reported that two genes required for normal chromosomal segregation in *Drosophila* code for adenosinetriphosphatase (ATPase)-activated contractile proteins. Thus, while we do not yet know the mechanism responsible for activating the homeotic genes sequentially in mammals, or whether chromosome segregation in mammals is similarly dependent on microtubule-mediated motors, it is clear that research on fruit flies and other model organisms can have direct relevance to studies on human embryos and that the advantages of different experimental systems can be exploited to tackle fundamental questions about both normal and abnormal human embryonic development.

In spite of the elegance of the genetic schemes currently being reported for *Drosophila*, it is important to realize that the mechanism for establishing axial polarity in the mammalian embryo may utilize different molecular processes. The mammalian oocyte is unique in that it does not acquire any of the intrinsic polarities characteristic of eggs of other animal species. Consequently, even up to the eight-cell stage of the embryo, each blastomere retains totipotent properties. The first indication of intrinsic polarity occurs when the trophoblast cell layer becomes segregated from the future inner cell mass. Even at this time, the inner cell mass cells appear to be equivalent to embryonic stem (ES) cells in that they lack a stable axial determination. Clearly, additional model systems such as the frog, in which growth factor concentrations control axial determination, the recently developed zebrafish system with its useful genetics, or the avian system, in which the polarization of the trophoblast establishes the initial axial pattern of the primitive streak, will be

important for elucidating the development of the human embryonic axis.

The development of the transgenic mouse system has opened up many new avenues for understanding both normal and abnormal mammalian development. Targeted mutagenesis of ES cells and their subsequent integration into the germ line of host mouse embryos have made possible the development of mouse strains deficient in genes important for key developmental processes. Thus, inactivation of the *wnt-1* gene (which is homologous to a key gene required in *Drosophila* for segmentation) results in loss of the midbrain, thus demonstrating the critical requirement for this gene. Similarly, this approach opens up the possibility of producing animal models of human diseases, either by introducing defective human genes into ES cells or by targeting the specific human mutation into the homologous mouse gene of the host ES cell, so that the disease process can be studied experimentally and new therapies developed.

In vitro manipulation of embryonic cell types is essential for identifying and studying specific cellular and intercellular processes active in a wide variety of cell types and tissues. Immortalized cell lines, representing stem cell populations as well as cells in varying stages of differentiation, have become important experimental materials for understanding developmental mechanisms. Similarly, immortalization of cell lines from mutant cells, such as mucosal epithelium of cystic fibrosis patients, provides new opportunities for elucidating the function of specific human genes.

## **Genetic Variation**

Genetic variation among races may affect the outcome of pregnancy under specific circumstances. The response of the mother and of the fetus to environmental insults and pharmacologic agents, as well as the response of the fetus to maternal disease and disease treatments, may all be influenced by genetic polymorphisms. These genetic effects may be compounded by cultural and socio-economic factors. In considering the research agenda outlined below, recognition of genetic diversity among women and their fetuses must be considered. Model systems, wherever possible,

must take into account the influences of normal genetic variation on developmental processes and also the fact that female mammals are genetic mosaics for polymorphic X-linked genes by virtue of random X-chromosome inactivation.

The recent advances that have been made in mapping genes in both humans and mice have revealed extensive syntenic regions in which the order of genes along the chromosome has been conserved. Thus, as genes are identified in mice, they can be cross-indexed onto human chromosomes and vice versa. The use of specific inbred strains of mice and crosses between them, together with new techniques for rapidly mapping genes, greatly facilitates the identification of multiple gene combinations affecting developmental processes such as fetal growth and birth weight. As the various genes are localized and identified in the mouse, it will be possible, because of the conservation of chromosomal organization described above, to predict where the genes are localized on human chromosomes.

In the discussion below, the next five sections relate to basic research needs. Then, beginning with the section on Prematurity, the discussion addresses priorities for clinical research.

## ***Key Issues/Research Recommendations***

### **Gene Activity During Gametogenesis and Development: Differences in Males and Females**

Most inherited genetic diseases follow the simple rule that a defective gene behaves identically regardless of whether it is inherited from the mother or the father. Basic research, in particular the study of mutant mice, has led to the unexpected discovery that some genes, normal and abnormal, behave differently depending on whether they are inherited from one parent or the other. In some cases, the maternal gene may be inactive in the offspring; in other cases, the paternal gene is inactive. This process, known as DNA “imprinting,” is now thought to involve far more genes than was originally supposed and almost certainly plays a role in determining the outcome of some inherited

diseases (e.g., the Angelman syndrome is produced when a deletion of human chromosome 15q11-q13 is inherited from the mother, but the Prader-Willi syndrome, which has a distinct phenotype, is produced when a similar deletion is inherited from the father). It is important to understand the molecular basis of imprinting, when it occurs in eggs and sperm, and how many genes it involves.

The process of reversible silencing of gene activity involves most genes on one of the two X chromosomes in female embryos at the stage of implantation. This "X-inactivation" mechanism of dosage compensation, however, is not complete. Genes that escape X-inactivation fall into four classes:

1. Genes in the "pseudo-autosomal" region of Xp that is regularly exchanged with a segment of the Y chromosome are truly identical in males and females (example: GM-CSF receptor  $\alpha$ );
  2. Genes that remain active when on the "inactive" X chromosome (examples: ZFX/ZFY and RPS4X/RPS4Y). These genes have equivalent but not identical functional genes on the Y chromosome;
  3. Genes that are still expressed on the inactive X to some extent but have no functional equivalent on the Y (examples: steroid sulfatase, Kallman syndrome gene). For these genes, females have two functional copies, while males have only one;
  4. Genes that are expressed only from the inactive X chromosome and are not expressed in male cells except during spermatogenesis (e.g., XIST). Their role may be limited to the X-inactivation process itself.
- Studies should determine the mechanisms of imprinting and identify imprinted genes in humans and mice.
  - A systematic exploration of genes expressed on the inactive X chromosome and genes expressed only on the inactive X chromosome could reveal fundamental differences in gene expression in males and females that are *not* directly related to sex development and hormones.

- Allelic differences at X chromosomal loci cause all females to be mosaics for two different cell lineages. Mosaicism for specific alleles, for example, at X chromosomal loci yet to be discovered, should be evaluated as possible contributing factors to the development of disorders that are either limited to females (example: Rett syndrome) or have a preponderance in females, such as autoimmune diseases, and also to gender robustness.

Once this basic science has been elucidated, researchers can apply this knowledge to clinical problems, such as those that pertain to implantation and placentation.

## Implantation and Placentation

The implantation of the embryo represents the initial intimate contact between conceptus and mother. The normal process of nidation and formation of the placenta is critical to the success of pregnancy. It establishes the link between the mother and fetus through which essential nutrients are exchanged. There are major consequences for maternal and fetal health when implantation is abnormal. Infertility resulting from fetal loss is common during the peri-implantation period. The success of assisted reproductive technologies is limited, to some extent, by an inadequate understanding of the implantation process. Ectopic pregnancy and placenta previa, which result from embryo implantation in abnormal sites, outside and within the uterine cavity, are significant causes of morbidity and mortality in women of reproductive age. Abnormal implantation (failure of invading trophoblast cells to remodel uterine arteries) has also been implicated in the pathogenesis of toxemia in pregnancy. Gestational trophoblast disease results from the dysregulated proliferation of trophoblastic cells. Placental insufficiency causes fetal growth retardation.

The processes of implantation and placentation are remarkable in that they encompass proliferation of the trophectoderm (the outer cell layer of the implanting embryo), the invasion of the trophoblasts into the uterine lining to establish the placental vascular bed, and the differentiation of trophoblast cells into a transporting epithelium, endocrine gland, and immunologic barrier that permits the fetus to be accepted as a semi-allograft.

The mechanisms underlying the normal process of implantation and placentation remain obscure. The agents that propel trophoblast replication and subsequent differentiation into the mature placenta are largely unknown. It is generally believed that these processes are driven by autocrine and paracrine mechanisms, but the catalogue of growth factors involved and their mode and sequence of action have not been delineated. The factors (e.g., proteases, protease inhibitors, and extracellular matrix proteins and cellular receptors for them) that control invasion and remodeling of the uterus during implantation are just beginning to be defined.

The development of the transport systems of the placenta, particularly the polarized syncytiotrophoblast, has not been explored at a molecular level. The regulation of genes that encode transport proteins, their level of expression, and the ways in which they are modulated by maternal nutrients and hormones have not been disclosed. The placenta produces a diverse repertoire of hormones, growth factors, and cytokines. The ways in which the elaboration of these substances is regulated and the functions of these factors in gestation are still poorly understood. Indeed, the physiological roles of hormones that have been known for decades are still uncertain (e.g., chorionic somatomammotropin). The mechanisms by which the trophoblast and fetus escape immune rejection are still unclear. Expression of unique histocompatibility antigens (HLA-G), the composition of immune cells in the uterus, and the production of immunomodulatory factors by the placenta may each contribute to the acceptance of the conceptus.

- Studies should determine the factors that drive placental growth and differentiation.
- Research needs to characterize the molecules involved in trophoblast attachment and invasion and elucidate their regulation.
- Investigations should clarify the differentiation of placental transporting and endocrine functions.
- Studies should investigate the mechanisms by which both placenta and fetus escape immunological rejection.

## Cell, Tissue, and Organ Differentiation

Abnormalities of development result in birth defects, which are at present the leading cause of infant mortality in this country. Molecular biology has ushered in a revolution in our understanding of how tissues acquire specific functions and how they organize into organs through hierarchies of gene expression. During embryonic development, new cell types are progressively generated in the progeny cells of the fertilized egg, with cells becoming more and more restricted in their developmental potential as tissues and organs approach their adult form. Certain cell populations, however, pause in this march to specialization, serving as transient, self-renewing stem cells that rapidly expand specific stem cell populations before moving on to the next stage of development.

Cell behavior during development is regulated by combinations of two basic strategies. In the first, genetic information dictating behavior is passed from parental cell to daughter cell in a discrete cell lineage. This lineage is established early in development by the expression of certain DNA-binding proteins, which in turn act on a group of diverse genes that influence cell phenotype. In the other strategy, cell behavior is dictated by nearby cells, which produce unique microenvironments containing a composite of extracellular matrix constituents (collagens, glycoproteins, and proteoglycans), growth factors, proteases, and protease inhibitors. Each of these classes of components represents several gene families that can differ depending on the cell type. The components interact with cell surface receptors (e.g., matrix receptors, growth factor receptors) and cell adhesion molecules, which are themselves part of the cell surface. The microenvironments create a molecular context that, as a result of cell surface interactions with multiple bioeffector molecules or with products of regulated activation pathways, causes signals to be generated within the cell that influence the developmental behaviors. Cell behavior during development is highly integrated, and the integration involves both strategies; a cell's responses to its neighbors will depend on its lineage and history and how it was previously influenced.

Understanding this developmental process has led to new insights into how organs such as the limbs, lung, and intestine acquire their form and function, but there are major research gaps. For instance, it is not understood how the basic organization plan of the human body arises. It is important to learn what produces the spatial arrangement of head-tail, front-back, and left and right axes.

- Studies should seek to discover how many different genes and components are involved in morphogenesis and the establishment of the basic body plan.
- Research should determine what mechanisms dictate the initial genetic change that leads to a cell lineage and what mechanisms subsequently serve to maintain a cell lineage.
- Investigations should determine whether embryonic and adult stem cells differ.
- Research should clarify the relationship of normal stem cell function to neoplastic stem cells.
- Studies should investigate how cell-specific microenvironments are established.
- Research should define the ways that microenvironments induce changes in developmental behavior.
- Studies should focus on how these mechanisms go awry in various birth defects (e.g., in congenital dislocated hip and anencephaly, which predominate in females).
- Investigations should explore the ways that these developmental behaviors are involved in the repair of tissue injury, whether in somatic tissues or in nerve regeneration, including the brain, where plasticity is evident.
- Studies should determine which developmental behaviors are altered in the action of various teratogens (e.g., thalidomide, retinoic acid, valproic acid, and alcohol).

- Research should clarify whether tissue-specific differentiation in the fetus can be accelerated or retarded to prevent or treat disease, analogous to the use of glucocorticoids to accelerate production of pulmonary surfactant in the near-term fetus.
- Investigations should determine whether the growth and differentiation of the vascular supply to a tissue can be induced or inhibited.
- Research should determine if the high-fidelity repair and remodeling of tissues performed by the fetus can be duplicated in the postnatal organism.

## Growth and Energy Metabolism in the Fetus

The mechanisms and factors involved in the regulation of fetal growth are poorly understood. Even though intrauterine growth retardation (IUGR) is a significant cause of mortality and morbidity in infancy, the control of fetal growth has not received the attention it merits in terms of the potential applicability of advances in knowledge to prevention or amelioration of this relatively common clinical problem. There are two major facets to consider: (1) inadequate nutrient transfer from the mother to the fetus (glucose, amino acids, fatty acids, glycerol, trace nutrients, and O<sub>2</sub>) for whatever cause, but most commonly from the reduction in utero-placental blood flow, and (2) the uptake and utilization of these substances for growth by the fetus to meet its energy requirements.

A variety of maternal and fetal factors influence these processes. Unlike postnatal somatic growth, which is regulated by pituitary growth hormone and thyroxine, fetal pituitary growth hormone, although found in high concentrations in the circulation, has a relatively minor role in fetal growth. Thyroxine influences central nervous system and skeletal development but has little effect on fetal growth.

Recent research suggests a major role of insulin-like growth factors-I and -II (IGF-I and IGF-II) and, quite likely, other growth factors—both known and unknown—on the growth of the fetus. Mice in which both of the IGF-II genes have been genetically

inactivated are born small and continue to have lower body weights throughout life. Research has shown parental imprinting of the IGF-II gene: the copy inherited by the embryo from the mother is inactive. After birth, pituitary growth hormone acting through its cell surface receptor generates IGF-I. The circulatory IGF-I arises mainly from the liver and has an endocrine effect on distant tissues; in addition, IGF-I is synthesized by many tissues, where it can act locally in a paracrine/autocrine manner. IGF-I acts through a widely distributed IGF-I receptor to induce its growth-promoting and metabolic effects. Both insulin and IGF-II bind to the IGF-I receptors, but with much lower affinity. It appears that the IGF receptors may also be imprinted, and specific mutations lead to impaired birth weight in mice (this is true of both IGF-I and -II receptors).

Insulin deficiency in the fetus leads to decreased fetal IGF-I production and impaired growth, whereas hyperinsulinism in the fetus (due to maternal diabetes mellitus, for example) can lead to fetal macrosomia. The effects of insulin are poorly understood, but its action on fetal growth appears to be mediated via the IGF-I receptor. In the fetus, insulin may serve to maintain a favorable homeostatic environment rather than acting as an important growth factor.

In addition, the major cell proliferative and metabolic actions of IGF-I and its metabolic clearance rate are modified by a family of IGF-binding proteins. Indirect evidence suggests that IGF-I is important (and possibly essential) for fetal growth. Direct evidence has demonstrated that IGF-II is essential. In the fetus, however, fetal pituitary growth hormone is not the critical mediator of circulating IGF-I. We have only the barest understanding of the regulation of fetal IGF-I and of other potentially critical growth factors. The concentrations of plasma IGF-I, glucose, and insulin, and the patterns of IGF-specific binding proteins and possibly IGF-II, can affect the concentration of circulating IGF-I in the fetus and in certain fetal organs. Hence, impaired transfer of critical substrates from mother to fetus or their decreased uptake by the fetus can suppress fetal generation

of IGF-I; this may represent an important mechanism for impaired growth of the fetus.

The concerted application of modern techniques of cell and molecular biology and of regulatory biology (systems physiology) should provide major insights into the mechanisms of normal and abnormal fetal growth. There are limitations to present experimental models of fetal growth retardation, all of which involve a comparative approach. For example, the nature of placentation is very different for primates as compared with all of the animal species below primates. Further, the two most commonly used species for studies of fetal growth retardation differ in their extent of maturity at birth: the rat (an altricial species) is immature at birth, whereas the sheep (a presocial species) is relatively mature at birth. Growth retardation has been produced in the rat and sheep fetus by compromising either utero-placental or umbilical vein blood flow by a variety of techniques or by restricting the nutrient intake of the pregnant ewe.

It is important to differentiate the metabolic, homeostatic actions of fetal hormones and growth factors from their influence on cell proliferation. For example, recent evidence suggests that fetal pituitary growth hormone may have significant homeostatic effects on glucose and lipid metabolism, but little effect on somatic growth. We need to pursue vigorously the potential differential effect of hormones and tissue factors on fetal metabolism and fetal growth.

The human placenta synthesizes and secretes two hormones that have metabolic and growth-promoting effects: a variant form of pituitary growth hormone (hGH-V) and chorionic somatomammotropin (hCS or placental lactogen). Both are secreted into the maternal circulation, but only hCS is transferred to the fetus and then in only relatively small amounts. The concentration of both hormones in the maternal circulation correlates with placental size. It has been postulated that both hormones affect maternal metabolism to help ensure an adequate supply of nutrients to the fetus and to increase the plasma concentration of maternal IGF-I. The placenta contains IGF-I and is a rich source of IGF receptors. The direct or indirect

actions of these two hormones on fetal growth and metabolism are still unknown.

In summary, both deficient or impaired transfer of nutrients across the placenta and impaired utilization of nutrients by the fetus due to poor intrauterine-placental blood flow lead to growth retardation. The fundamental mechanisms governing fetal growth and the roles of maternal, placental, and fetal growth factors, their cellular receptors, and the circulating growth hormone and IGF-binding proteins and their regulation are promising areas for research.

- Studies should be conducted on the genetics of parental imprinting of fetal growth factors and receptors (IGF-II, IGF receptors) and multifactorial effects of imprinting.
- Research needs to exploit modern techniques to assess qualitative and quantitative aspects of growth factors, their receptors, their binding proteins (where pertinent) in normal and abnormal growth, and their direct and/or indirect effects on fetal growth.
- Studies should employ the spontaneous occurrence of abnormalities of human “growth hormones” and growth factors and their respective receptors and binding proteins to dissect their role in fetal growth retardation.
- Researchers should explore the relative roles of different nutrients in fetal growth and energy metabolism.

### ***Intrauterine Growth Abnormalities, Habitual Abortion, and Toxemia (Pre-Eclampsia)***

Recent developments in the early diagnosis of intrauterine growth failure, the optimal timing of delivery, and modern neonatal care have improved the short- and long-term outcomes for infants with intrauterine growth failure. However, subnormal fetal growth continues to contribute to fetal loss, perinatal mortality, neonatal morbidity, and poor long-term development.

The cocaine epidemic together with polydrug use (including alcohol) and smoking and their deleteri-

ous effects on fetal growth may be important determinants of the recent increase in the low-birth-weight rate among Black infants. The determinants of ethnic differences in birth weights are not fully understood.

There are two additional known causes of abnormal fetal growth: pregnancy-induced hypertension (toxemia or pre-eclampsia) and diabetes mellitus. The pathophysiology of toxemia remains obscure. This disorder has significant consequences for mother and fetus. Maternal diabetes is associated with an increased incidence of fetal abnormalities including disordered growth (macrosomia). The management of the pregnant diabetic is complex, requiring early identification of diabetes by testing for abnormal glucose tolerance and vigilant monitoring.

### ***Habitual Abortion and Toxemia***

Women with lupus anticoagulant (LAC) or anti-cardiolipin (ACA) syndrome will probably not have clinical manifestations other than unusual pregnancy wastage and multiple thrombotic events at an early age (prior to age 60). The relationship of toxemia to the presence of such autoantibodies needs further study. In addition to ACA, LAC, and the antibodies that mediate biologically false-positive serologic tests for syphilis (BFP-STS), antibodies to vascular endothelial cells and abnormalities in T lymphocyte subpopulations have been reported in women with toxemia. Why this disorder occurs more often in the primigravida is also unknown. In addition to morbidity for the pregnant woman, this condition results in intrauterine growth retardation. An increased risk for toxemia has been reported in women with certain HLAs (HLADR4), but has not been confirmed in other studies. Recent success in treatment of toxemia associated with LAC and ACA by intravenous immunoglobulin further emphasizes the etiologic relationship between the presence of these antibodies and the clinical problem, and such therapy deserves further study.

- Studies need to determine how substance abuse and smoking influence intrauterine growth and whether their effects are reversible if the postnatal environment and nutrition are optimized.

- Investigations should explore the biochemical (molecular) basis of the pathophysiology of toxemia.
- Research should define biochemical and molecular predictors of risk for toxemia.
- Improved therapeutic measures for toxemia need to be developed.
- Research should find better methods for detecting and managing maternal diabetes mellitus.

## Development of the Nervous System

The nervous system has been singled out for special consideration for several reasons. First, it is the initial major organ system to be established during embryogenesis, and its development continues throughout gestation: neurons begin to develop, and connections between them are made beginning in the middle of the first trimester; these processes continue into the postnatal period.

Second, the nervous system is, by every measure, the most complex of all the body's organ systems. In the adult, it comprises thousands of different kinds of neurons, each of which develops a characteristic phenotype and forms highly specific connections with other neurons and with peripheral target tissues. The successful elaboration of both the neurons and their connections is the consequence of the complicated interplay of developmental factors that are both intrinsic and extrinsic to the embryonic nerve cells and their precursors. Because of both the extended time period during which neural development proceeds and its complexity, the developing nervous system is particularly vulnerable to insult from a variety of sources.

Finally, and most important, it is devastating when the nervous system fails to develop normally. Anomalies of the central nervous system account for over half the congenital abnormalities that are incompatible with life. Babies who are born with nervous system defects suffer from varying degrees of compromised motor, cognitive, and emotional function. That we can see, hear, speak, and move is a consequence of countless developmental events correctly executed in the embryonic nervous sys-

tem. The same applies to those characteristics that we believe make us "human," including consciousness, creativity, and humor. The consequences of abnormal nervous system development not only compromise the child's future but also, and equally important, place a lifelong burden on the mother or other care-givers.

There are now unprecedented opportunities to elucidate normal developmental processes in the nervous system, to explore how and when these processes go awry, and to consider therapeutic interventions. First, new methods have been developed to trace lineage and the development of connectivity. The application of fetal surgery to primates and to felines has allowed investigators to examine mechanisms. Second, the blossoming of molecular neurobiology has resulted in the cloning and identification of genes that may play crucial roles in the developing nervous system. This effort has been expedited by the realization that molecules identified in model systems such as *Drosophila* and nematodes have counterparts in mammals. Finally, two vertebrate systems, the zebrafish and the mouse, offer exceptional promise. The zebrafish embryo is accessible for both observation and manipulation. The ability to generate transgenic mice and perform gene knockout experiments provides the opportunity to explore mechanisms in the previously inaccessible nervous system of the fetal mammal and promises to revolutionize our understanding of these important developmental processes.

There are major gaps in our understanding of how the brain develops. The first recognizable step in this process is neural induction—the diversion of cells in the ectoderm that would otherwise have become skin cells, to differentiate into the tissues of the nervous system instead. Although the key elements in this process have been identified, we do not know the molecular basis of this process, nor do we know how the anterior/posterior and dorsal axes are established. One of the hallmarks of the mature nervous system is the complexity of its anatomical organization and the diversity of neuronal phenotypes. There are striking differences in the morphological and functional properties of different regions along the neuraxis. The cerebral vesicle at the rostral end

of the neuraxis yields cortex (and cognition), while the caudal region of the neuraxis yields spinal cord (and simple reflexes). How these differences are generated is unclear. It is known that in many parts of the nervous system, lineage (a neuron's family history) does not determine its fate. Rather, in a small number of cases, evidence has accumulated that environmental factors determine phenotype. The cellular and molecular mechanisms responsible, however, are virtually unexplored. The cerebral cortex is a special case with respect to these processes. It seems likely that a developmental program common to all neocortical areas gives rise to a "proto-cortex" that is uniformly laminated. The emergence of a particular cytoarchitecture is the result of incoming input (sensory, associational, etc.), with subsequent refinement once activity begins in the circuits. How this is accomplished is not known, nor is it known how substances of abuse, such as alcohol and cocaine, influence these processes.

Within each brain region, there is a characteristic pattern of proliferation, differentiation, and death. How these first two processes are controlled is largely unexplored. One striking aspect of neurogenesis is that the generation of neurons in each brain region occurs in a relatively restricted time period and that different neuron classes are generated in an orderly pattern. In contrast, the role of growth factors in supporting neuronal survival is well established. As in the hematopoietic system, particular molecules may play distinct roles in different temporal and spatial settings, possibly controlling proliferation, survival, and differentiation.

The establishment of neural circuits requires remarkable pathfinding and recognition. Growing axons navigate long distances over increasingly complex routes, to appropriate targets where growth ceases and functional connections are established. The cellular mechanisms and molecules involved in these processes are just beginning to be identified in simple systems, and their roles need to be explored in the context of mammalian development.

Although these research gaps have been identified in the context of neural development and

pregnancy outcome, answers to these questions have profound implications for repair of both the injured and the aging nervous system. Since women live significantly longer than men, they appear to experience increased susceptibility to the neurodegenerative diseases and dementia. Pathfinding mechanisms and growth factor biology may contribute to enhanced regeneration, and growth factor biology is likely to yield therapies for neurodegenerative diseases. Finally, the developing nervous system is remarkably malleable. We now know that although this plasticity decreases after the fetal period, it is not lost completely. Better understanding of the biological basis of plasticity and the mechanisms that are responsible for its partial loss could allow us to reaccess these developmental programs when necessary.

- Studies should investigate the mechanisms responsible for neural induction and early pattern formation, which are unknown at present.
- Research should define the mechanisms by which brain regions—including those of the cortex—and cell fates are specified.
- Investigations should clarify the factors at work in the control of neural cell proliferation, differentiation, and death and also characterize the molecules involved.
- Studies should define the mechanisms that are responsible for the establishment of functionally appropriate circuits.

## Prematurity

The infant mortality rate in the United States is higher than that of most developed countries, mainly due to the high incidence of preterm births. The U.S. weight-specific survival of low-birth-weight infants is excellent—indeed, the best in the world—but too many of these infants are born to minority Americans. Moreover, the economic and emotional costs of neonatal intensive care are enormous, and the subsequent growth and development of survivors in many cases is less than optimal. The birth of a preterm child who is sick may also have deleterious effects on

maternal well-being and family life. There is thus an urgent need to prevent preterm birth.

The risk factors for prematurity, including sociodemographic factors, lack of prenatal care, and substance abuse, are established. Unfortunately, the normal process of parturition is poorly understood. As a consequence, there is no good framework for comprehending the pathophysiology of preterm labor and the means by which it can be prevented, predicted, and treated.

- Data from distinct demographic regions are needed to understand the societal factors that predispose the preterm birth.
- Research should evaluate strategies for prevention of prematurity through health education and delivery of prenatal care. Those strategies found to be effective should be implemented.
- Studies should identify the biological and social factors that underlie the significant differences among races resulting in marked differences in the percentages of preterm births.
- Investigations should delineate the factors that determine the onset of parturition in women, including how infection and drugs promote premature labor.
- Effective pharmacologic agents for regulating premature uterine activity need to be developed.

## **Teratology and Environmental Factors**

Normal fetal development is a major concern to women during their pregnancies. At present, there is no means of experimentally establishing the teratogenic potential in humans of a drug, chemical, virus, physical agent, occupational exposure, or stressor. Use of animal models is generally of little help because teratogenicity is not readily extrapolated between species. A variety of such influences impinge on the fetus, and countless women avoid such exposure—even when it is necessary for economic or other reasons—to prevent potential harm to their fetuses.

For most drugs approved by the Food and Drug Administration, safety in pregnancy has not been established because pregnant women are excluded from new-drug testing. Women may, therefore, be deprived of needed treatment while pregnant because of lack of information. Alternatively, women on drug treatment who have accidentally become pregnant may make unnecessary decisions to abort their fetuses.

Pharmacogenetics, the study of inherited (i.e., genetic) variation in response to pharmacologic agents (e.g., the rates of oxidation or acetylation), explains why not all drugs and chemicals to which pregnant women were exposed result in an adverse outcome to their pregnancies. For example, less than 10 percent of fetuses exposed to hydantoin, given to the mother during pregnancy to control seizure disorders, will develop the recognized “fetal Dilantin syndrome.” The risk to the fetus depends on the fetal genotype, specifically, the activity of an enzyme, epoxide hydrolase, that inactivates a toxic drug metabolite.

Research is needed to develop methods to establish the true teratogenic potential of various agents in human pregnancy.

- Controlled studies should evaluate the risk to the fetus of essential medications.
- Prospective data should be collected by following up pregnancies with documented exposures to not only prescription drugs but also to environmental or occupational toxins or mutagens.
- Researchers should develop means to enhance the predictive value for humans of animal experimentation.
- In vitro test systems for teratogenicity that are valid predictors of teratogenic potential in humans need to be developed.
- Researchers need to find ways to investigate drug metabolism in pregnancy.
- Studies should clarify the influence of fetal and maternal genotypes on drug metabolism.
- Investigations need to determine the role of the placenta as a barrier to drugs and their metabolites.

- Investigations should clarify the biochemical basis of drug action on fetal development.

## Fetal Monitoring

Birth defects are now the major cause of infant deaths in the United States. Therefore, methods that determine risk and that detect and possibly correct these defects are needed. Human embryos and fetuses can be monitored for abnormal genotype, karyotype, and morphological development at different stages of gestation and by different methods. Screening of pregnant women by non-invasive technology, regardless of specific risk factors, currently includes second-trimester blood tests for alpha-fetoprotein (AFP), which is elevated if the fetus has a neural tube defect or congenital nephrosis, and reduced in trisomies (e.g., Down's syndrome); for human chorionic gonadotropin (hCG), which is elevated cases of trisomy; and for unconjugated estriol, which is low in cases of trisomy, fetal immaturity, and maternal smoking. Abnormal screening test results do not necessarily imply fetal abnormality but do serve as an indication for more definitive studies on amniotic fluid and cells.

At present, a variety of fetal tests are possible. Real-time ultrasonography in the middle-trimester detects morphological abnormalities of organ development in addition to assessing fetal age and viability. Pregnancies at risk for specific genetic disorders (e.g., single-gene defects responsible for muscular dystrophy or cystic fibrosis and chromosomal imbalance syndromes) are monitored by testing fetal cells obtained by amniocentesis (at 14-16 weeks of gestation), early amniocentesis (11-12 weeks), chorionic villous biopsy (9-11 weeks), and cordocentesis (midtrimester percutaneous umbilical blood sampling) for molecular, biochemical, or chromosomal abnormalities.

The existing methods for monitoring fetal development are not sufficiently precise, are relatively expensive, are not highly accessible to the population at large, and in some cases pose a risk to the pregnancy.

- Researchers need to develop effective noninvasive methods to monitor fetal growth and development.

- Studies should focus on the development of simple procedures to isolate fetal cells from maternal blood samples for diagnostic tests (e.g., PCR-based DNA diagnosis of specific gene defects and fluorescent in situ hybridization for chromosome imbalance), with the ultimate goal of automating these procedures so that they can be applied to population screening.
- Methods need to be developed for detecting fetal abnormalities early in gestation to enable intrauterine treatment.
- Follow-up studies should evaluate the reactions of couples to test results and the outcome of monitored pregnancies (including research into the ethical issues of decision-making).
- Researchers need to improve preimplantation embryo diagnosis by blastomere biopsy.
- As genes responsible for inherited disorders are identified at an increasing pace, methods to identify gene carriers and to monitor their pregnancies need to be established and evaluated, along with relevant ethical issues.

## Special Issues

### Training Recommendations

We are entering a new era in which the explosion in knowledge of molecular embryology can be applied to the developing human, thereby preparing it for better adaptation to extrauterine life and allowing the precise detection of genetic abnormalities earlier in development. These advances will require that obstetricians and neonatologists learn the language of basic developmental biology and molecular genetics to be able to communicate with basic research scientists and to draw from this new knowledge, both conceptually and methodologically. Thus, these research physicians must obtain indepth training in several basic science disciplines. Equally important, these research physicians and the basic science labs supporting and training them must be provided with enhanced opportunities for research funding to apply their unique knowledge to problems relevant to pregnancy outcome. The Office of Research on Women's

Health (ORWH) should establish training programs for postresidency fellows in pediatrics and obstetrics and gynecology who wish to obtain basic research training in developmental biology, genetics, or other fundamental sciences.

This program should augment the successful NIH-sponsored Pediatric Scientist Training Program

(PSTP), Reproductive Scientist Training Program (RSTP), and the Physician Scientist Awards. It can be supported by funds from industry as the PSTP and RSTP are, but administered by the ORWH with the involvement of academic role models. Consideration should be given to funding the trainees for research following their training period to ensure that they get a successful start.



## AGING PROCESSES

*Cochairs:*  
*Shiriki K. Kumanyika, Ph.D.*  
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In recent years, the concept of aging has undergone radical revision. Growing older, it is now recognized, does not mean a universal and inevitable decline in physiological and psychological function. Instead, different organs, different systems, and different individuals age at different rates. This great diversity has clinical implications: it suggests that, in many cases, there may be opportunities to devise interventions to enhance the health, functioning, and sense of well-being of individual older women. In particular, new knowledge that many bodily systems and functions, as well as characteristics such as personality traits, change little or not at all in “normal” aging allows health care practitioners to assume that many of the adverse changes seen in elderly patients—for example, in salivary gland function—are indicators of some pathological condition. Such a condition, once diagnosed, may well be amenable to therapeutic intervention.

The reasons for this variability in patterns of aging are not understood. It is not known why some women (and men) are able to retain relatively good functional capacity into their later years, while others

experience progressive or even sudden decline in function. While the decline in capacity to function observed to varying degrees in older people has, in previous years, been attributed simply to irreversible aging processes, it is now becoming apparent that for individuals who do note dramatic changes as they grow older, many of these alterations are not primarily due to the aging process itself. Rather, they are the result of a complex interaction among disease (both current conditions and the consequences of diseases that occurred in earlier years), lifestyle, nutrition, psychological status, and social support. The observed differences in extent of aging among individuals derive in some complex way from an interplay among these factors, some of which help individuals to maintain function, while others can potentially rob a person of capacity to function.

However, in spite of individual differences, levels of disability among the general population do, as a general rule, rise with age, particularly after age 75. For example, one prospective study found that 30 percent of previously independent elders lost independence in function during a 6-year period

and that persons who were over age 85 at first contact had three times the risk of death or loss of independence.<sup>1</sup> In study subjects over age 85, there was also seven times the risk of institutionalization as compared with all the elderly people studied. Major functional impairment is present in approximately 5 percent of persons ages 65-74, and 35 percent of those 85 and older (National Center for Health Statistics).

Further, the ratio of women to men rises progressively above the age of 65. Projections indicate that in the year 2020 there will be 69 men for every 100 women at age 65, and 36 men per 100 women at age 85.<sup>2</sup>

Other statistics underscore the excess burden of growing older among women as compared with men. Women report higher levels of disability than men, spend more years in the disabled state than men (this is in part related to their longer life expectancy), are in greater need of support because of widowhood, and make up a substantially higher proportion of the nursing home population. In 1985, for example, there were 963,900 women in nursing homes, as compared with 334,400 men.<sup>3</sup> Further, National Health Information Survey data for 1990 indicate that, among a total population of slightly more than 7 million women over age 75, nearly 2 million were reported as unable to carry on a major activity or limited in the amount or types of major activities they could perform.

The major challenges for research, therefore, are to achieve a full understanding of how the various factors involved in aging—physical, cognitive, and psychosocial—adversely affect the individual, both separately and combined and to identify as well those factors that serve to protect individuals against the effects of growing older, especially disability. In addition, the precise link between various phenomena of aging and the development of functional limitations will have to be determined. Finally, the relationship between functional limitation and a capacity for independent living will have to be investigated more fully.

In addition, studies will be needed to illuminate the important differences in attitude toward aging

in women and the effects of aging on women in diverse socioeconomic status (SES) groups and racial and ethnic populations. Knowledge about such differences will help in planning more effective intervention and prevention strategies for the various populations and may also reveal some significant protective factors that might provide a significant benefit if applied to the population as a whole.

To achieve a complete understanding of these factors, it is therefore necessary to study cohorts of women that include individuals who have aged with little compromise in physical or cognitive functioning as well as those who have some level of disability.

It is not yet known to what extent many of the causes and consequences of aging can be prevented, or even reversed, but new knowledge offers tantalizing hints that much of what is now associated with aging can be delayed for many years—perhaps indefinitely. However, achieving this goal will require intensive efforts to understand the complexities of the interplay among the many factors that collectively lead to the negative aspects of aging.

## **Major Themes**

The major causes of disability in persons under age 80 appear to be related to specific diseases rather than to the aging process itself. Beyond age 80, a variety of noncardiovascular disorders, including arthritis, dementia, and neurosensory disorders, account for an increasing burden of disability. From the perspective of health promotion, the implications regarding the reversibility of these various causes of disability, and the capacity to motivate the changes in behavior that can modify them, may be very different. However, in the old-old (women over age 85), the relative contributions of cardiovascular diseases versus other degenerative diseases to the age-related burden of disability is not documented. Further, the burden of the aging process itself, as opposed to behavioral or environmental causes (e.g., poor housing and limited transportation), can substantially affect overall function in ways that have yet

to be fully clarified. In addition, the relationship among gender, race, and SES is poorly understood.

The need for information on these issues is illustrated by reports issued by two recent Institute of Medicine (IOM) panels that addressed the major causes of disability and attempted to trace linkages among diseases, risk factors, social factors, and disability (*Setting a Research Agenda for Aging and Health Promotion for the Second Fifty Years*). The panel members were unable to find sufficient research data to provide a specific focus for their reports on disability. For this reason, they recommended that epidemiologic studies be undertaken to determine better the causes and course of disability in older persons.

From a health policy perspective, such knowledge is essential, because the rapid growth of the oldest age groups in our society is certain to bring an exponential growth in disability rates in the future. Because of the inadequacy of the current data on disability, it is difficult for policy-makers today to project future disability rates in older cohorts. In fact, there is still substantial disagreement about whether disability rates will be lower or higher in subsequent cohorts of persons of advanced age. For these reasons, better epidemiologic data on the antecedents, risk factors, protective factors, and natural history of age-related disability are needed for planning long-range policies that pertain to the elderly.

Epidemiologic data would also have clinical implications. Clinicians are increasingly recognizing that the link between a disease/disorder and disability is not always obvious because of the multiplicity of factors involved in determining health status in the elderly. Therefore, classifying an older person simply by disease nosology does not furnish an adequate estimate of functional status; older persons with the same disease and apparently similar severity may have differing functional status because of the combined impact of a constellation of other aging-related factors.

Measures of function, such as timed tests of manual performance, may be more predictive of subsequent use of long-term-care services than actual classification by disease state. A 1988 position

paper from the American College of Physicians states that “assessment of the impact of illness on physical, mental, and psychosocial functioning is an essential element of clinical diagnosis, a major determinant of therapeutic choices, a measure of their efficacy, and a guide in the planning of long-term care for the dependent elderly.”

In spite of this recommendation, it is not clear that these assessments are being performed in clinical areas. For example, a randomized trial of providing functional information to community internists concerning their patients (69 percent were female and 32 percent were over 70 years of age) did not produce differences in the patients’ functional status or health outcome measures.<sup>4</sup> Other recent data<sup>5</sup> indicate that physicians are unaware of the functional status of their elderly patients when those patients are discharged from the hospital. Recognizing this need to assess the impact of illness, combined with the surprising lack of utilization of this information in clinical applications, creates opportunities to apply information from population-based longitudinal studies to clinical areas.

Thus, information concerning the link between diseases/disorders and disability would benefit the understanding of disability. It would also have important implications for health policy analysis, plans for medical and social services, and clinical approaches to the problems of elderly women.

However, population-based longitudinal data on function and disability in older women are sparse, and the course of physical disability in older women is poorly characterized at present. Most of the data concerning disability in the population are based on cross-sectional data and are therefore subject to limitations in the ability to calculate incidence of disability as opposed to its prevalence, distinguish adequately between preceding factors (especially psychological ones) and factors that result from disability, and measure the rate of longitudinal changes. Prospective studies of specific disease categories have been performed and provide examples of the lessons that can be learned from such a study. For example, one study of cataract surgery demonstrated that a medical intervention can produce a functional change not only in physical status, as would be expected, but also in mental status.<sup>6</sup> This change in mental health was

maintained for over a year. Subsequent follow-up of the study population at yearly intervals for 4 years demonstrated that independent living in the community was maintained in 90 percent of the participants after the medical intervention.

The methodology for assessing functional status in older persons is improving and is applicable to population-based epidemiological studies as well as to intervention studies. Scales that address physical function, cognitive function, emotional status, social activities, and social support are available.

This methodology has thus created an opportunity to compile measures of health status and multidimensional function, which can be used to test specific hypotheses. However, this manner of proceeding must be carefully applied to particular populations under study. There are a number of measurement issues related to validity and reliability, sensitivity to change, threshold effects, the utility of self-reports, interview responses versus observed performance, and the use of proxy respondents. In addition, many design and conceptual issues must still be resolved. Dissecting out the complex effects of age-related functional decline, disuse, and disease- and degenerative disorder-related decline will require rigorous measurement and tracking, sophisticated systems with explicit criteria for making distinctions, and vigilant surveillance.

## ***Key Issues/Research Recommendations***

### **Physical Aspects of Aging**

Much more needs to be learned about the natural history of healthy aging, especially in women. For example, new evidence shows that the risk of dying from heart-related causes increases steadily with age in women, as in men. This smooth, linear increase with age suggests that there is no threshold effect around the age of menopause; in other words, menopause, as distinct from age, has no effect on death from coronary heart disease.

In order to provide the comprehensive baseline required for assessing the health of women as they age, longitudinal studies need to be conducted on large cohorts of women, with women from diverse racial, ethnic, and SES groups, to obtain a full picture of the natural history of

healthy aging in women, including those factors that serve to protect against negative outcomes such as disability, and also to determine the usual range of variation in divergence from healthy aging. Research is also needed to inventory and investigate the causes for any gender-related differences in the patterns of aging that emerge in these longitudinal studies.

Also, the natural history of sensory loss and alterations in perception needs to be better understood, along with their role in functional impairment and associated disability. Any gender-related differences in such perceptions at birth, as well as the patterns of their loss over time, need to be clarified to provide a reliable background against which to assess the results of more detailed studies.

- Studies should inventory and investigate the causes for any gender-related differences in patterns of aging.
- More basic research studies are needed on the array of causes of aging and how these interact to produce the phenotype of aging, at all physiological levels—cell, organ, organ system, and whole organism. Understanding the mechanisms by which aging is regulated requires careful dissection of changes that may occur at the cellular level and of how these changes affect the whole organism. For example, more work needs to be done to clarify the possible role of therapies such as the antioxidant vitamins A, C, and E and human growth hormone in mitigating the processes of aging.
- Studies should identify the genetic determinants of longevity in women, determine whether there is a genetic factor that protects against severe chronic diseases such as Alzheimer's disease and Parkinson's disease, and elucidate the role of genetic factors in the senescence of the immune system.
- Particular emphasis should be placed on research into the senescence of the immune system because this system shows important declines with advancing age that are responsible for an increase in the number and severity of acute infections as well as a loss of ability to inhibit tumor growth and an increase in the appearance of abnormal

antibodies that react against one's own body (autoantibodies). Older women in particular are more prone to production of autoantibodies, which have been implicated in the etiology of chronic diseases such as systemic lupus erythematosus and rheumatoid arthritis.

- Investigations should establish the early signs of significant chronic conditions in women, such as atherosclerosis, and determine whether these signs differ in quality and quantity as compared with men.
- More research is needed on the chronic conditions that predominantly affect women, such as osteoporosis, to learn the extent to which these conditions are unavoidable concomitants of aging versus the consequence of inheritance and health-related behaviors.
- Research should determine whether the skeletal changes that occur during pregnancy predispose to musculoskeletal disorders in later life.
- Studies should explore the gender-related differences in trauma-induced dysfunction in early life and their possible impact on age-related musculoskeletal disorders in later life.
- The long-term effects of scoliosis need to be quantified.
- Investigations should analyze the alterations in female bladder and urethral physiology that occur with changes in hormonal status with aging.
- Studies should seek to understand the decline in homeostatic reserves that occurs with aging and that leads to frailty.
- More work is needed to learn the consequences of multiple prior illnesses in older women—how do sequelae from these conditions affect the physical health of these women, their mental functioning, and their ability to carry on the activities of daily living?
- Investigations should determine the effect of the sequential addition of chronic conditions as women age. For example, how does a diagnosis of diabetes affect a woman who has already had

rheumatoid arthritis for several years in terms of both her physical health and her capacity to maintain independence?

- Studies should focus on the range of factors that result in the higher incidence of certain chronic conditions among women as they age. Examples of such factors include physiological, behavioral, SES, and cultural/racial/ethnic variables. For instance, National Health Interview Survey data for 1979-81 show that diabetes among persons over age 75 (expressed in terms of rate per 1,000 persons) was 168.1 for Black women (versus 72.6 for Black men) and 89.8 for white women (versus 79.5 for white men).
- Studies should investigate the role of exercise in promoting healthy aging in women. It is important to learn optimal exercise regimens for women with different levels of fitness, and especially for women with disabilities.

## Cognitive Function

- Studies should determine the natural history of functional cognitive decline or improvement with age.
- Research should determine whether women are at greater risk for Alzheimer's disease than are men.
- Since women undergoing estrogen treatment show a lower than expected rate of dementia, studies should explore whether estrogen has a prophylactic effect for dementia.
- More research is needed to understand whether changes in cognitive function are different across populations.
- Studies should examine the relationship among levels and changes in basic cognitive abilities and/or neuropsychological processes and associated health practices and behaviors as aging progresses—for example, compliance with medication regimens.
- Methods are needed to determine normative and pathologic changes that precede dementia, and also to clarify any gender-specific components of the precursors to dementia.

## Postmenopausal Hormone Replacement Therapy

When levels of ovarian hormones are deficient, postmenopausal women may be at risk for accelerated bone loss and therefore subject to greater risk of fracture, coronary heart disease (due in part to changes in cholesterol and other factors), and symptoms such as hot flashes and urinary incontinence. Major studies on the safety and efficacy of replacement therapy have recently been published: for example, the role of postmenopausal estrogen therapy in reducing the risk of coronary heart disease was examined in 48,470 postmenopausal women.<sup>7</sup> The risk was found to be significantly reduced among women with either natural or surgical menopause, although estrogen use was not associated with any change in the risk of stroke. In spite of the results of these new studies, some important questions about the estrogen replacement therapy persist.

- Basic research should clarify the mechanisms of the action of exogenous estrogen and progesterone on (1) bone—to learn how these hormones interact with growth hormone and other local growth factors, (2) the heart—to clarify the ways that these hormones achieve their cardioprotective effect, and (3) the arterial wall—current evidence suggests that exogenous estrogen protects the arterial wall against atherosclerosis.
- Studies should investigate the effects of the addition of progestin to exogenous estrogen preparations on coronary artery disease risk factors and coronary artery disease itself.
- Clinical trials should determine the optimal type, route, dose, and timing of estrogen and progestin treatment to maximize the benefit and minimize risks.
- More research is needed to learn how estrogen and progestin treatment are influenced by age and body type. Both amount and type of body fat are influenced by sex hormones and contribute to risks of high blood pressure, diabetes, and heart disease.

## Osteoporosis

Osteoporosis places an enormous burden on the health of the older women in the United States, especially among women over the age of 70. The overwhelming majority of hip fractures occur among this group; each year, 200,000 people are hospitalized and temporarily disabled as a result, and a significant proportion of these individuals suffer long-term disability.

- More research is needed on the efficacy of different combinations of treatment regimens, using currently available modalities such as calcium supplementation, estrogens, and exercise, among women in different age groups.
- Studies should investigate hormonal stimulation of bone formation in older women, testing, for example, growth hormone, growth hormone plus estrogen, and insulin-like growth factor.

***"Hip fractures are the most serious consequence of osteoporosis. Of those with hip fractures, one-third will become totally dependent, one-half will never again walk independently, and one-half will experience social deterioration. One out of every five will not survive beyond the first year after the hip fracture."***

Sandra C. Raymond, Executive Director, National Osteoporosis Foundation

- Dietary supplements should be tested for their capacity to stimulate the release of growth hormone and whether it is possible to restore the normal pattern of periodic secretion using this factor.
- Studies should clarify the ways in which the osteoporosis disease process differs in women age 70 and over as compared with the development of osteoporosis in younger people.

## Dementia

In nearly every population-based study, the prevalence of Alzheimer's disease is found to increase with age, and is higher in women than in men at nearly every point in time. There is also a dramatic increase in the incidence of Alzheimer's disease among the old-old—primarily a female population—to the extent that it has been postulated that Alzheimer's disease is becoming nearly universal with advanced age.

- Studies are needed to clarify whether women are at greater risk than men for Alzheimer's disease at different points along their life span but especially at the most advanced ages.
- Research should investigate whether estrogen treatment has some prophylactic effect on dementia because women undergoing estrogen treatment have been found to have a lower than expected rate of dementia.
- Autopsy studies could be used to determine the possible linkage between Alzheimer's disease and some of the changes in brain anatomy associated with menopause and ovariectomy, for example, the neuronal hypertrophy in the infundibular nucleus. Some evidence suggests that this represents an adaptive response to the loss of circulating estrogens.
- Clinical trials should determine whether there are gender-related differences in response to the drugs for Alzheimer's disease currently in development, such as tacrine and physostigmine salicylate.

## Cancer

Among women age 65 and older, there are disproportionately high rates of cancer incidence and mortality.

- Research should investigate the role of factors associated with aging in women, such as the decline in the immune system, that increase older women's risk of developing cancer.

- Studies should clarify whether currently available anti-cancer drugs, as well as those under development, have different pharmacokinetics in women as compared with men and especially in older women.
- Research is needed to learn more about what factors (e.g., genetic, behavioral, cultural) result in the observed differences in the incidence of cancer and cancer mortality among women in the various racial and ethnic groups.

## Heart Disease

In 1987, total cardiovascular disease accounted for 5.170 million years of potential life lost before age 75. In addition, more cardiovascular disability is expected because many people who have had effective treatment for coronary artery disease and prevention of atherosclerosis at age 40 to 60 will develop cardiovascular diseases later in life.

Until recently, cardiovascular diseases in women have not been recognized as a serious health problem, particularly by women themselves. However, heart disease is in fact the number one killer of American women: of the more than 500,000 deaths from heart attack each year, approximately half occur in women. Nearly one in two female deaths in the United States is from cardiovascular diseases. Women do develop heart disease later in life than men; approximately 90 percent of all heart disease deaths among women occur after menopause, that is, after the age of 50. While one in nine women ages 45-64 has some clinical cardiovascular disease, the rate climbs to one in three at age 65 and older.

*“There remain misconceptions about how women die in this country. Heart disease continues to be considered a ‘man’s disease,’ but cardiovascular illness is the largest killer of women . . . .”*

*Deborah I. Dingell, Chair, Board of Directors, National Women’s Health Resource Center*

- Studies should investigate why women may be less successful at altering the various risk factors associated with heart and blood vessel disease, especially smoking. During the past 20 years, there has been a 20 percent reduction in the number of male smokers but only a 6 percent reduction among women.
- Research is needed to learn how much time is required after cessation of smoking before the risk attributable to smoking disappears in women; previous studies of smoking cessation have focused primarily on men.
- Studies should clarify the role of alterations in lipoprotein levels that accompany menopause. Low-density lipoprotein (LDL) levels are lower in premenopausal women as compared with men of the same age but higher in postmenopausal women than their male counterparts. However, some data from animal studies indicate that LDL may be less atherogenic in females than males, the possible result of an—as yet—undetermined protective effect from endogenous estrogen.
- Studies should determine why high triglyceride levels are better predictors of coronary risk in postmenopausal women than in men of comparable ages. Researchers also need to learn why, conversely, high-density lipoprotein (HDL) levels are higher in women and, at any given level, provide more powerful protection in women than in men.
- Investigations should determine why the lipoprotein risk factor lipoprotein(a), high levels of which are usually correlated with the risk of heart disease, occurs in higher concentrations in women.
- Studies should clarify why diabetes is such a powerful risk factor for atherosclerosis in women.
- More research is needed to discern the reasons why lifestyle interventions such as low-fat diets, weight loss, and exercise have appeared to be less effective in lowering lipoprotein levels in women as compared with men. In particular, the role of endogenous gonadal hormones in modulating these responses needs to be investigated.
- Studies should examine the interplay among several risk factors for heart disease in women, especially the effects of oral contraceptive use in women who also have diabetes or lipoprotein abnormalities.
- Studies are needed to delineate the full roster of cardiovascular risk factors in women, which may differ considerably from those in men.
- The important differences in the manifestations of atherosclerotic diseases in women versus men need to be fully explored.
- Because most of the drugs used in coronary disease were initially evaluated in men, new studies on the relative safety and efficacy of these drugs for women need to be conducted. For example, women usually have smaller coronary arteries than men, so fluctuations in vasomotor tone in these arteries may be more important; therefore, nitrates and calcium channel blocking agents may be a preferred therapy in women.

## Nutrition

- Studies are needed to determine the causes and consequences of weight loss and undernutrition in older women.
- The causes of the greater increases in adiposity in Black and most other minority women need to be explored and compared with men and white women across the life span.
- Research should investigate whether the protective effects that being mildly overweight have on bone health in older women are sufficiently important to warrant revision of weight standards for older women.
- Studies are needed to assess the role of sensory loss (e.g., of taste and smell) in changes in dietary patterns among older women.
- Research should assess whether changes can be made in nutritious prepared foods to make them more appealing to older women.

- Nutrition studies should investigate the possibility that acceptable food supplements can be developed that would help ensure that older women receive a healthful diet.
- The psychosocial determinants of dietary behavior in women need to be determined (e.g., living alone versus living with a family or group).

## Disability

### ***Measuring Disability***

- Research is needed to develop a precise definition of disability.
- Tools are necessary to differentiate women all along the spectrum of functioning.
- More sensitive measures are required to assess limitations at preclinical levels of impairment at a time when they may be more amenable to intervention.
- Studies should find ways to identify those women who are at high risk.
- Methodologies are required to assess role performance as a measure of disability.

### ***Disability Versus Maintaining Function***

Research is needed to determine the extent to which psychosocial and environmental factors play a crucial role as either risk factors or protective factors in helping women maintain function as opposed to becoming increasingly disabled over time.

- Studies should investigate the role of a family or social support system in physical and mental decline.
- The roles of educational level and income as intervening variables in the production or prevention of impairment and disability need to be investigated.
- The physiological effects of widowhood need to be clarified.
- The specific occupational risk groups and factors that result in total disability need to be elucidated.

- Studies should compare the role of the older woman in families of diverse ethnic populations as compared with the majority population: Black, Native American, Asian, and Hispanic.
- Research is needed to determine how the health goals of women at different stages along the life span influence maintenance of function.

### ***Prevention of Disability***

Researchers need to develop prevention strategies that can minimize or eliminate functional impairment and associated disability in women.

- Studies should identify the reversible areas of functional decline that occur with aging.
- Research is needed to develop measures to restore or improve functions that have declined and to maintain functioning at the highest level possible for as long as possible.
- Investigations should clarify the precise role of adhering to a healthy lifestyle in preserving good functioning into advanced age.
- Rehabilitative services need to be developed to meet the particular needs of older women with multiple chronic disabilities.
- Studies should determine what factors give rise to the compensatory mechanisms used by women to cope with disability.

## ***Special Needs***

Understanding the processes at work in the phenomenon of aging in women is uniquely dependent on a sequence of research, beginning with basic investigations aimed at building a sound base of comprehensive knowledge about the changes that occur at the cellular level as women age. A central research question is the relationship between senescence of cells in culture and aging of the individual, in particular, how changes in the ability of human cells to replicate in culture may be related to the age of the cell donor.

A study of the replicative capacity of 600 fibroblast cultures derived from skin biopsies of women

and men enrolled in the Baltimore Longitudinal Study of Aging (BLSA) revealed that the major decrease in the replicative potential of cells from both men and women occurs after the third decade of donor age.

More research to augment cell cultures sampled longitudinally (as in the BLSA) is needed to clarify the precise mechanisms underlying cellular senescence in various kinds of cells and organ systems. Then studies can begin to examine how these changes affect more gross-level aspects of aging, such as alterations of the immune system and susceptibility to acute and chronic disease. Finally, this knowledge will serve as the requisite background for assessing effects on aging of more external factors such as racial/ethnic population, SES level, and availability of support systems.

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## CARDIOVASCULAR FUNCTION AND DISEASE

*Cochairs:*

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**A**lthough a 1986 workshop<sup>1</sup> generated a surge of new research activity on issues related to the cardiovascular health of women, important questions remain about the pathogenesis of atherosclerosis and coronary heart disease (CHD) in women.

The age-adjusted death rate for all cardiovascular diseases (CVDs) among women declined markedly between 1963 and 1983. Nevertheless, deaths from CVDs still account for one-half of all deaths among women; each year, 245,000 women die from CHD. The fact that 64 percent of deaths resulting from CHD in women occur in nonhospitalized patients is of particular importance. Figure 1 depicts the numbers of deaths among U.S. women from eight major causes.

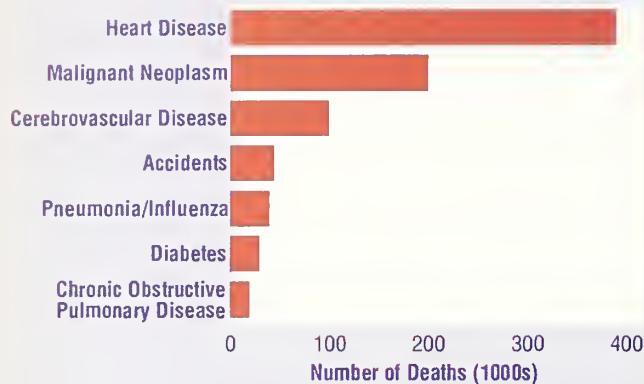
As this figure shows, heart disease is by far the principal cause of death. Figure 2 shows schematically the death rates associated with CHD in the United States according to age and race. Rates of death from CHD are higher among Black women than among white women up to the age of 75 years, but higher among white women thereafter. In

addition to the cost in lives, CVDs of women involve major expenditures for both the individual and the Nation. Those costs are summarized in Figure 3.

Major differences exist in the seriousness of CVD among various racial and ethnic groups of women: mortality from CVDs is more significant in Black women than in white women (Figure 4), for example. Current thinking attributes this disparity to differences in systolic blood pressure and amount of body fat.

Another intriguing racially related phenomenon is a difference in the effect of hypertension treatment in Blacks versus whites, in terms of mortality (Figure 5). Antihypertensive therapy markedly reduces mortality in Black women but not in white women. It is unlikely that the Black/white difference in mortality relates to racial differences to the extent it does in atherosclerosis (Figure 6). Despite the fact that diabetes is common among Native American women, Hispanic and Native American women have remarkably less CHD than white women (Figure 7). The mechanisms of protection are not understood.

**Figure 1.**  
**Leading Causes of Death Among Women  
 of All Ages (U.S., 1983)\***



\* Modified from Thom TJ. Cardiovascular Disease Mortality among United States Women. In: Eaker ED (ed). *Coronary Heart Disease in Women. Proceedings of an NIH Workshop*. New York: Haymarket Doyma; 33-41, 1987.

From the National Center for Health Statistics: *Vital Statistics of the United States*.

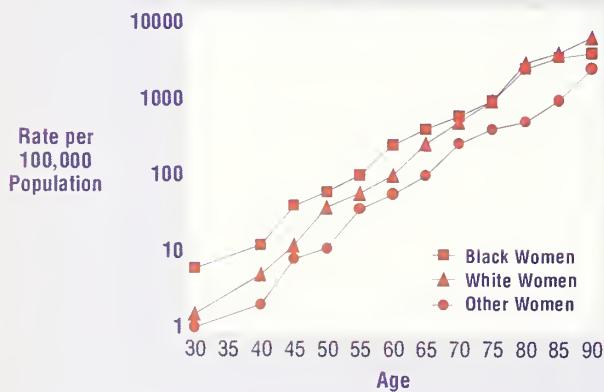
## Major Themes

Research directed to the identification and modification of risk factors for CVD, including behavioral, cultural, and socioeconomic factors, has been conducted primarily among male populations. Risk modification strategies as well have been evaluated primarily in male populations. Limited information is available on the role of behavioral, cultural, and socioeconomic factors in the etiology or primary and secondary prevention of CHD in women. Similarly, limited information is available on the strategies most useful in effecting change in risk behaviors among various subgroups of women. Yet, some current research suggests that women may differ from men in terms of these factors, for instance, in their physiologic response to stress, increased responsiveness to behavioral risk modification, and poorer compliance with postcoronary rehabilitation programs. Poor compliance has also been noted among female patients on hormone replacement therapy (HRT), a potential risk modifier unique to women.

Several risk factors are similar in both men and women; however, little is known about the magnitude of their effect on CVD among women. For example, data suggest that coronary disease is more likely in women and men who work in subordinate positions—where they are able to exert little control over their jobs—as compared with individuals in more managerial positions; women are more likely to be in subordinate than in managerial positions. The impact of the increasing numbers of women entering and remaining in the work force on the prevalence of CHD is not known nor have we learned whether workplace modifications could alter cardiovascular risk among women.

Myocardial infarction is nearly always caused by thrombosis of an atherosclerotic plaque in a coronary artery. Stroke is also often secondary to thrombosis, with ischemic stroke resulting from an embolism of intracardiac thrombi or platelet thrombi that have formed on carotid artery plaques. Thus, identifying which factors influence the formation of coronary and carotid thrombi is very important. Unfortunately, epidemiologic studies of CVD have included very few women.

**Figure 2.**  
**Death Rate Associated with Coronary Heart  
 Disease According to Age and Race  
 (U.S. 1980)\***



\* Modified from Thom TJ. Cardiovascular Disease Mortality among United States Women. In: Eaker ED (ed). *Coronary Heart Disease in Women. Proceedings of an NIH Workshop*. New York: Haymarket Doyma; 33-41, 1987.

From the National Center for Health Statistics: *Vital Statistics of the United States*.

The Framingham study did report a positive relationship between fibrinogen and risk of CVD for women. More recently, the Atherosclerosis Risk in Communities (ARIC) study has collected baseline data on hemostatic factors on more than 8,600 women and more than 7,000 men (roughly 25 percent of each group is Black) and is making gender, race, and age comparisons. Separate analyses for men and women have been carried out on lifestyle factors and lipid parameters associated with fibrinogen and factor VII. No data are yet available on incident cardiac disease, but an association of fibrinogen with ultrasound-detected thickening of the carotid artery has been found. This finding has not yet been examined for gender differences. The ARIC group is also analyzing its female population for relationships between hemostatic factors and menopausal status and hormone use. In this regard, the NIH-sponsored Postmenopausal Estrogen/Progesterone trial (PEPI) is examining the effects of different postmenopausal hormone regimens on fibrinogen as a primary end point and on other hemostatic parameters as secondary end points and non-hemostatic system end points in a population of postmenopausal women.

Various antiplatelet regimens have been used in studies on patients after myocardial infarction or with transient ischemic attacks. Only about 25 percent of these patients were female, and in many instances the results were not broken down by gender. However, the Canadian Stroke Study found that men obtained benefit from aspirin, while women did not. On the other hand, an overview report on 25 studies of stroke or myocardial infarction prevention showed that there was no indication of the number of women in the various trials nor were any gender differences noted among respondents.

Secondary prevention of myocardial infarction with warfarin was widely studied from the 1950s to the 1970s but then fell from favor. Recently, the question has again been investigated, but no data on women in particular are available.

The several large trials in which thrombolytic therapy has been evaluated have studied men in

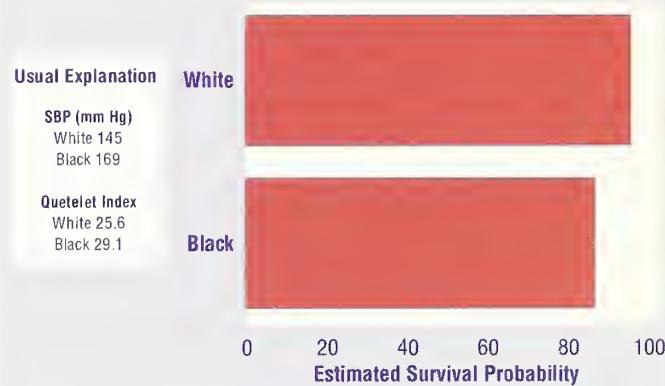
**Figure 3.**  
**Ambulatory Visits/Hospital Admissions Per Capita and Total Costs for Cardiovascular Diseases of Women in 1980\***

Condition	Number of Women (1,000s)	Per Capita Cost	Total Cost in Dollars
Cardiovascular Disease with Hypertension	1,982	\$2,327	\$4,612,114,000
Cardiovascular Disease without Hypertension	2,635	2,486	6,550,610,000

\* Modified from Harlan, WR. Cardiovascular disease care for women: service utilization, disability, and costs from the National Medical Care Utilization and Expenditure Survey. In: Eaker ED (ed). *Coronary Heart Disease in Women. Proceedings of an NIH Workshop*. New York: Haymarket Doyma: 55-61, 1987.

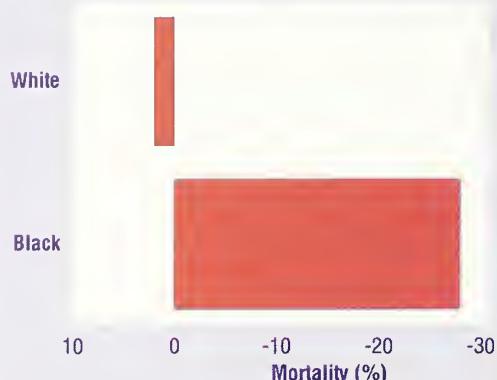
NOTE: The annual cost impact to the Nation for cardiovascular diseases of women is estimated to be \$11.2 billion.

**Figure 4.**  
**Cardiovascular Disease Mortality in Women Aged 40-64 Years\***



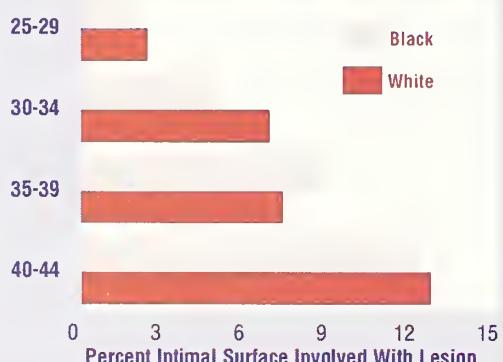
\* Modified from Johnson JL, Heineman EF, Heiss G, Hanes CG, Tyroler HA. *Am J Epidemiol* 123: 209-19, 1986.

**Figure 5.**  
**Effect of Race on Mortality of Women After Treatment for Hypertension\***



\* Based on data from the NHLBI Hypertension Follow-up Program - data from Shapiro and Rutan. Modified from Clarkson TB. Session II Highlights: Pathophysiologic Processes of Atherogenesis. In: Eaker ED (ed). *Coronary Heart Disease in Women. Proceedings of an NIH Workshop*. New York: Haymarket Doyma; 11-19, 1987.

**Figure 6.**  
**Differences in Coronary Artery Atherosclerosis Between Black and White Women\***



\* Modified from Newman WP III. Gender and Racial Contrasts of Atherosclerosis. In: Eaker ED (ed). *Coronary Heart Disease in Women. Proceedings of an NIH Workshop*. New York: Haymarket Doyma; 133-5, 1987.

overwhelming proportion (80 percent). The GISSI and ISIS-2 studies both suggested that the outcome in women was worse than in men. One recent

TIMI II study has indicated that major or minor hemorrhage (but not major hemorrhage alone) was more common in women who received tissue plasminogen activator and were assigned to the study's conservative strategy than in men who received the same treatment.

CVD is most likely to affect the older woman, who is likely to be a family care-provider herself. The effect of CVD on the older woman in relation to family functioning, on her provision of care (or interruption thereof) to other family members, and on costs associated with the disruption to the family caused by the woman's disease, is unknown.

Any examination of risk factors or risk modification among women needs to consider the impact of culture and socioeconomic status (SES). Risks are manifested differently among different subgroups. Women in low socioeconomic groups are likely to have greater morbidity and a poorer outcome than women in other SES strata. Women in Mexican American and Native American populations are at greater risk for diabetes yet are less likely to experience morbidity from diabetes mellitus, which contributes to excess morbidity among white women. Black women treated for hypertension are less likely to experience morbid events than are white women. The behaviors of these subgroups need to be examined to determine whether selected factors inherent in the ethnic/cultural/SES group are protective (for example, social support networks) or injurious (for example, nutritional habits).

Efforts are clearly needed to develop more effective interventions for the treatment of obesity. It is also important to identify specific subgroups of the obese population and develop special programs for these women. Interventions aimed at the prevention of obesity in those at increased risk and at reducing the incidence of major weight gains among women are needed. The behavioral and physiological determinants of upper-body-fat obesity and approaches to modifying body fat distribution remain to be determined.

Finally, there is a pressing need to examine carefully the nature of current cardiac rehabilitation programs, which have, in the main, been designed for men. In particular, research should focus on learning the reasons why many women fail to participate in these programs.

## Estrogen Replacement Therapy and CVD

The long-term effects of estrogen replacement therapy have received increased attention due to the many clinical ramifications of this treatment for a growing number of female patients. A previous report from the Lipid Research Clinic's ongoing study of over 2,200 women demonstrated that, after 8 years of follow-up, women using estrogen at baseline had a two-thirds reduction in mortality from CVD compared with nonusers. After 14 years, women using estrogen were found to have significantly lower total mortality (47 percent) and mortality from CVD (63 percent). Cancer mortality was also lower in users (19 percent) (Figure 8). Estrogen had a protective effect for women with and without known risk factors for CVD. Estrogen use had a protective effect in nonsmokers and ex-smokers as well as in current smokers. Perhaps more important, estrogen use appears to override known risk factors for death from CVD. Estrogen users who smoked had the same risk of CVD as nonsmoking women who did not use estrogen.

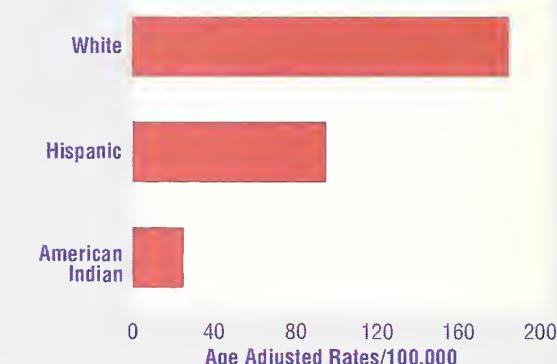
The same pattern was seen in normotensive women versus hypertensive women and in women of normal weight versus overweight women.

Statistical adjustment for smoking, hypertension, and high- and low-density lipoprotein (HDL and LDL, respectively) levels did not alter the significant protective effect of estrogen use on CVD risk. These results suggest that estrogen use reduces the risk of CVD over the long term. Also, estrogen may have a protective effect through mechanisms other than changes in lipoproteins.

## Key Issues/Research Recommendations

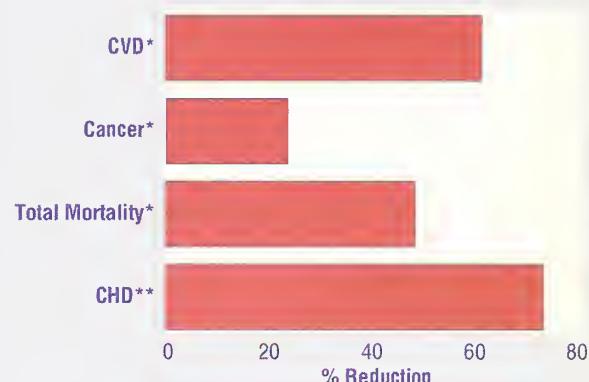
Not enough is known about CVD in women; this deficit may reflect an inappropriate prioritization of medical resources biased in favor of male patients. Some general theoretical approaches, as well as specific disease areas, are highlighted below. Each of the areas mentioned is of considerable import, although specific prioritizations may vary within the scientific community.

**Figure 7.  
Ethnic Differences in Coronary Heart Disease Mortality Among Women\***



\* Based on death certificate data from residents of New Mexico. Modified from Becker TM, Wiggins C, Key CR, Samet JM. *Circulation* 78:302-9, 1988.

**Figure 8.  
Reduction in Mortality of Women Who Were Estrogen Users Versus Nonusers**



\* From data presented by Trudy L. Bush at the 31st Annual Conference on Cardiovascular Disease Epidemiology based on results from the Lipid Research Clinics 14-year Follow-Up Study.

\*\*Based on data from the Nurses Health Study modified from Stampfer MJ, Willett WC, Colditz GA, Rosner B, Speizer FE, Hennekens CH. *N Engl J Med* 313:1044-9, 1985.

Figure 9 indicates the priority assigned to CVDs based on an estimate of their importance to the health of women. Also shown are priorities for research on the modulators of those CVDs.

**Figure 9.**  
**Cardiovascular Disease Priorities  
for Women's Health and Research**



## Clinical Entities

### Clinical Cardiovascular Disease

The gender differences in CVD, which span the continuum from clinical practice to understanding basic mechanisms, have been inadequately explored, in part because of the false assumption that atherosclerosis is less prevalent and more benign in women. Nevertheless, the available data suggest gender differences in areas ranging from risk factor identification and modification to diagnosis and treatment. For example, it is puzzling that sudden death from ventricular fibrillation tends to occur with equal frequency in men and women, yet at the same time, women have a higher mortality rate after myocardial infarction that is not solely attributable to more advanced age.

In addition, medical resources appear to be used less by both female CVD patients and their physicians, perhaps because of some gender bias, overuse by male patients, or in recognition of the inadequacy of diagnostic testing and therapeutic procedures. Recognizing and correcting these gender differences are necessary to under-

stand the mechanisms of CVD fully and to provide equivalent quality of care to all patients.

- Investigations should explore the risk factors and their interactions for all forms of CVD, including CHD, cerebrovascular accidents (CVA), and peripheral vascular disease (PVD) in women.
- Studies should investigate strategies to produce risk factor modification and the effects of modification of risk factors on primary and secondary CVD. Particular attention should be paid to both positive and undesired effects of intervention, as well as to differences in response and compliance among ethnic and socioeconomic groups.
- Research needs to examine gender differences in relation to myocardial and vascular function (in both healthy women and those with disease states), left ventricular hypertrophy, congestive heart failure, migraines, Raynaud's phenomenon, and coronary spasm. This should include evaluation of coronary vasomotor reserve in normal and atherosclerotic women, with and without hormone replacement therapy.
- Studies are needed to improve understanding of factors affecting consideration of and access to primary and secondary treatment of CHD in women. This should include better patient-physician communication and improved appreciation of the importance of CHD in women.

### Coronary Artery Disease

- The procedures for clinical diagnosis of coronary artery disease (CAD) in women need to be improved. Research should focus on better descriptions of anginal syndromes, enhancing the efficacy of diagnostic and screening testing in women, and developing alternative diagnostic strategies.
- Studies should investigate the mechanisms that result in women's poorer outcomes after myocardial infarction and coronary revascularization procedures and how to correct these problems.

- Research needs to examine the efficacy of components of the cardiac rehabilitation effort on outcome after myocardial infarction, including factors that affect women's success in such programs.

### **Stroke**

Perhaps because rates of stroke have declined rapidly in the United States during the current century, this condition has received considerably less attention than CAD. By 1985, the United States ranked seventh lowest for age-standardized rate of stroke mortality in women among 27 developed countries and third lowest in men.

While men have about a 30 percent higher death rate from stroke than women, this obscures the fact that stroke may be a more important factor in women's health. Stroke in the United States accounts for a higher percentage of deaths in women than men, in all stages of life, and stroke mortality rates among U.S. Black women are almost twice those of white women. Since stroke mortality rates increase with age, the biggest discrepancy is seen in those age 85 or older, among whom stroke accounts for 12 percent of mortality in women, compared with 9 percent in men. Data also consistently indicate that young women have about a 50 percent excess of subarachnoid hemorrhage, the least common form of stroke. Estimates of morbidity are much harder to obtain, but according to the National Hospital Discharge Survey, women had about 15 percent fewer hospital discharges for the first-listed diagnosis of stroke than men in 1980 but a 6 percent higher rate in 1989.

Evaluation of trends in strokes is complicated by problems of diagnosis and classification. Ischemic stroke is classified using several overlapping systems, which makes it difficult to compare results across studies.

Smoking, dietary fat, serum cholesterol levels, blood pressure, postmenopausal hormone replacement, and use of aspirin have all been associated (positively or negatively) with the incidence of ischemic stroke. Besides these atherosclerotic risk factors, risk factors for ischemic stroke associated with female gender include pregnancy, autoim-

mune diseases, mitral valve prolapse, oral contraceptive use, migraine headache, and chronic atrial fibrillation. Case series of carotid endarterectomy suggest that women are less likely to receive this preventive intervention; two studies, of 206 and 221 consecutive cases that included both sexes, included 26 percent and 27 percent women, respectively. For cerebral hemorrhage, elevated blood pressure and heavy alcohol use are the only consistently documented risk factors, although aspirin use may also have a role.

Data from several community-based studies in the United States and Europe suggest that stroke rates may have started to increase in the 1980s in both sexes. Other recent population-based reports from the United States have shown a decrease in the rate of decline in stroke mortality, a reversal of the male majority in hospital discharge rates for stroke, and an increase in hospital discharges for stroke in both sexes in the two most recently reported periods (1988 and 1989). If true, this trend could be due to increased diagnosis of less significant events since the advent of the computed tomography (CT) and magnetic resonance imaging (MRI) scanners. However, it could also reflect higher stroke rates in older persons, especially older women, a rapidly growing demographic segment.

- Investigations should explore the reasons behind the possible recent increase in incidence of stroke and stroke subtypes in women.
- Research should clarify the impact of stroke on disability and dependency in women, especially older women.

### **Peripheral Vascular Disease**

Peripheral vascular disease, like stroke, is complicated by a lack of generally accepted standards for diagnosis and nomenclature. However, a preliminary stratification between venous and arterial disease is easily accomplished. Relatively few studies have addressed the epidemiology of these diseases.

Venous disease can be subdivided into superficial and deep anatomic locations. Varicosity is by far the most prevalent of the superficial conditions.

Its incidence increases with age and is about 50 percent more common in women than men, with a prevalence of about 80 percent in women over age 60. While rarely associated with medical complications, this condition does account for substantial health care costs.

Deep venous thromboses (DVTs) have more serious medical implications, but before the advent of duplex ultrasonography, the study of this condition was quite limited. One study found no gender differences in the incidence rates or anatomic locations of DVT, but the women included were significantly older and had a higher rate of unilateral single thrombi.

Peripheral artery disease (PAD) is associated with other life-threatening disorders. Independent of these associations, PAD itself accounts for substantial and costly morbidity. Diagnostic standards are lacking for this condition, which complicates interpretation of the literature. Population studies have had conflicting results regarding gender differences in the prevalence of PAD when this condition is defined exclusively by symptoms but not when assessments are made by blood pressure or Doppler flow measurements. In the comprehensively studied Rancho Bernardo cohort, the prevalence of large-vessel PAD was 11 percent in women at an average age of 66 years.

However, large-vessel PAD is an extremely potent independent risk factor, doubling the risk of cardiovascular death after 10 years in women (Framingham study) and making cardiovascular death five times more likely in both sexes (Rancho Bernardo cohort). Despite these findings, a report based on National Hospital Discharge Survey data from 1985-87 found that hospital discharge rates for PAD in men were 30 percent higher than those in women.

Isolated small-vessel PAD, a separate entity affecting arterioles 2 mm or less in diameter in the absence of large-vessel disease, was more prevalent than large-vessel disease (16 percent versus 11 percent in women) in Rancho Bernardo and more than doubled the risk of cardiovascular death. It is not associated with the usual athero-

sclerotic risk factors and may represent a vaso-spastic process.

- Studies are needed to standardize the diagnostic criteria for large- and small-vessel PAD, determine the prevalence of PAD using those definitions, and validate the relationship between those definitions and clinical events.
- Research should determine the prevalence of DVT and its relationship to other concomitant disease and future clinical cardiovascular events.
- Assessments must be made of the economic and functional costs of superficial venous disease and of possible population-based prevention measures to reduce them.

### ***Hypertension***

- Studies should investigate the efficacy and risks of antihypertensive treatment in women and subgroups of women (defined by characteristics such as race and age). Differences in neuroendocrine profiles may provide strategic guidance and should be considered.
- More research is needed on the causes and risks, both maternal and fetal, of pre-eclampsia and underlying essential hypertension in pregnancy. Prenatal screenings for risk factors and nutritional guidance should be more widely available than at present.

### ***Sudden Cardiac Death***

- Investigations are needed to analyze the possible differences between men and women in the etiology of sudden death. Women appear to have a lower prevalence of CHD, but ventricular fibrillation is more common in women than in men. These differences should be analyzed both epidemiologically (by reexamination of existing data bases) and pathophysiologically, with special emphasis on therapeutic implications.

### **CVD Risk Modulators**

#### ***Sex Hormones***

Multiple factors moderate the expression of CVD among women. These factors include, among others, hormonal influences, concurrent disease, be-

havior, sociocultural, ethnic, and socioeconomic factors. Most of these factors do not operate in isolation; they interact. Each is important and should be addressed in future research.

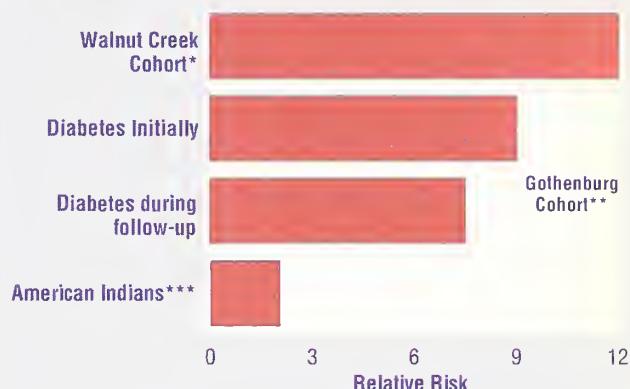
- Studies should clarify the usefulness of hormone replacement therapy for primary and secondary treatment of CVD in women, including:
  - addition of progestins;
  - optimal dose and duration for prophylaxis;
  - optimal dose and duration for treatment;
  - concomitant use of lipid-lowering drugs;
  - effects on cognitive function;
  - identification of risk-factor subsets deriving greater or lesser benefits—HDL, atherogenic LDL, high lipoprotein(a);
  - examination of the factors that influence non-compliance with HRT among women;
  - concomitant use of low-fat diets.
- Research is needed to clarify the pharmacodynamics and tissue effects of estrogens and progestins, with particular attention to newer compounds.
- Studies should examine the effect on women's CHD risk and risk factors arising from the natural variability in endogenous estrogen levels in both premenopausal and postmenopausal periods.

### **Diabetes Mellitus**

Diabetes mellitus is associated with a two- to three-fold increase in CVD mortality; it is the leading cause of death in both type I and type II diabetes. The increased cardiovascular mortality is especially prominent in diabetic women (Figure 10). Interestingly, Native American women appear to be protected against the effects of diabetes on CVD (Figure 10).

The mortality rate from acute myocardial infarction is higher in diabetic patients and is 25 percent higher in diabetic women than in men. The

**Figure 10.**  
**Effect of Diabetes Mellitus on Cardiovascular Disease Mortality of Women**



\* Based on 8,935 premenopausal women. Modified from Periman JA, Wolf PH, Ray R, Lieberknecht G. *Am J Obstet Gynecol* 158:1568-74, 1988.

\*\* Modified from Lapidus L, Bengtsson C, Blohme G, Lindquist O, Nystrom E. *Acta Med Scand* 218:455-62, 1985.

\*\*\* Based on New Mexico Navajo Indians and Arizona Pima Indians. Modified from Coulehan JL, Lerner G, Helzlsouer K, Welty TK, McLaughlin J. *AJPH* 76:412-4, 1986 and Nelson RG, Sievers ML, Knowler WC, et al. *Circulation* 81:987-95, 1990.

risk of cardiovascular death in the survivors of myocardial infarction after 6 years of follow-up is 40 percent higher in diabetic than in nondiabetic subjects, perhaps due to poor glycemic control.

Multiple risk factors for macrovascular disease, such as hypertension, obesity, hyperglycemia, hyperinsulinemia, microalbuminuria, elevated levels of fibrinogen, quantitative lipid and lipoprotein abnormalities, and altered platelet function, are frequently present in diabetic individuals. However, there have been no trials in which assessment of cardiovascular mortality was performed in diabetic patients after modification of some of these risk factors.

These factors do not by themselves explain the increased prevalence of CVD in diabetics and do not explain why white diabetic females lose the protective effect against CVD usually conferred by their sex. Some risk factors, such as triglyceride levels, may be more important in diabetic than in nondiabetic subjects and in women in general. A few reports, performed in a small number of individuals, suggest that lipoprotein(a) levels are increased in diabetics and that they are closely

related to glycemic control. Furthermore, qualitative alterations of some lipoproteins considered to be atherogenic are common in diabetes, and they may contribute to the increased prevalence of CVD in diabetes. Finally, a greater propensity to formation of antibodies against modified lipoproteins and subsequent formation of immune complexes exists in diabetes. This may lead not only to foam cell formation but also to activation of macrophages and the release of cytokines, which would further enhance the acceleration of atherosclerosis. Whether these alterations are present more commonly in diabetic women than in men, and whether menopause is a factor, needs to be determined, as well as whether these alterations can explain why diabetes constitutes an independent cardiovascular risk factor.

- Investigations should examine alterations in lipoprotein metabolism in diabetic women. Particularly relevant are studies investigating LDL and HDL subclasses and their respective cellular metabolisms; lipoprotein(a) levels; and susceptibility to modification (glycation and oxidation) and the possible consequences of modifications to these lipoproteins on lipoprotein metabolism and in promoting antibody formation (i.e., endothelial damage, platelet activation and aggregation, macrophage activation, and foam cell formation).
- Studies are needed to identify CHD, CVA, and PVD risk factors (e.g., lipoproteins, insulin resistance, fat distribution, free fatty acids) and determine their relative importance in diabetes mellitus. The effects of modification of the most important risk factors on primary and secondary CVD should be discussed.
- Research should investigate the metabolic consequences and cardiovascular implications of different routes of insulin administration. Cholesterol ester transfer protein (CETP), important in lipoprotein metabolism, decreases among both diabetic women and female monkeys receiving insulin intramuscularly or subcutaneously. An important current hypothesis is that insulin delivered directly to the liver via a pump would restore function of CETP.

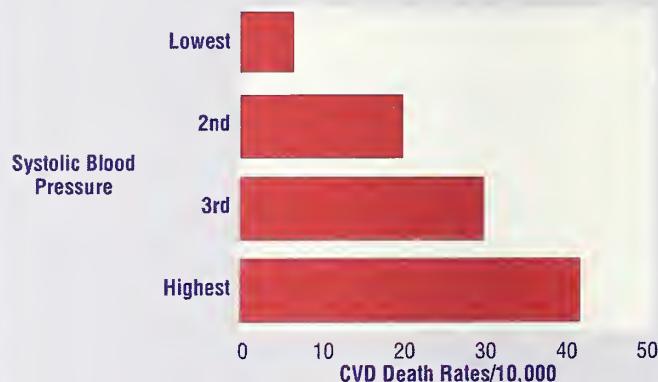
- Studies should examine the effects of estrogen, hypoglycemic drugs, lipid-lowering drugs, and antioxidants on lipoprotein metabolism and vascular wall function.
- Researchers need to find ways to prevent the occurrence of diabetes, including both behavioral and pharmacological interventions.

### Hypertension

Before menopause, systemic hypertension is significantly less common in women than in men; thereafter, however, its prevalence in women increases dramatically, reaching levels significantly higher than those in men of comparable age. Systolic blood pressure has been shown to be a major risk factor for CVD in women (Figure 11). This is true for both naturally occurring menopause and menopause produced by surgery or other artificial means.

Whether the menopause-related increase in blood pressure is related to estrogen withdrawal, over-production of pituitary hormones, unopposed actions of adrenal androgens, weight gain, and/or a combination of these factors and other as yet undefined neurohumoral influences is currently the subject

**Figure 11.**  
**Cardiovascular Disease Death Rates of Women By Quartiles of Systolic Blood Pressure\***



\* Modified from Bush TL. Cardiovascular Disease Mortality in Women: Results from the Lipid Research Clinics Follow-up Study. In: Eaker ED (ed). *Coronary Heart Disease in Women. Proceedings of an NIH Workshop*. New York: Haymarket Dyma; 106-11, 1987.

of both fundamental investigation in animal models and clinical trials. This is an increasingly important clinical problem because of the aging of the population and the extremely high prevalence—up to 80 percent—of hypertension in elderly women.

Oral contraceptive-induced hypertension and pregnancy-induced hypertension occur only in premenopausal women. Oral contraceptive use is associated with a small but significant increase in blood pressure in users compared with nonusers, but the reasons for this are not well understood. Both pre-eclampsia and underlying essential hypertension in pregnancy are associated with increased fetal morbidity and mortality, but adequate treatments for these disorders are lacking, and their pathogenesis is unclear.

- Studies are needed to clarify the basic mechanisms by which hypertension alters vascular wall function to promote atherosclerosis in women.
- Studies should investigate the effects of oral contraceptives on normotensive and hypertensive women and the possible pressor effects of hormone replacement therapy in hypertensive women.
- Research is needed to evaluate the effects of behavioral risk modification directed to hypertension management on subsequent morbidity and mortality among white and Black women.

### ***Thrombosis and Thrombolysis***

- Studies should evaluate the effects of antiplatelet therapy and anticoagulation on secondary prevention of CVD in women, through reevaluation of existing data and new intervention trials.
- The data from all trials of thrombolysis should be reanalyzed to determine efficacy and risks in women. In addition, data that suggest decreased access to thrombolysis treatment in women need to be verified and, if correct, such practices should be altered.
- Research is needed to investigate gender differences and sex hormone effects in thrombosis/thrombolysis and endothelial cell and vascular function.

### ***Psychosocial Factors***

- Gender-specific methodologic tools must be developed for measuring psychosocial variables in women, if there is no norm in the referenced data or if a given tool has a poor predictive validity for women.
- Studies should evaluate the contribution of individual attributes such as traits and emotions (e.g., hostility, depression, or stress reactivity) to CVD risk and recovery from CVD events in premenopausal and postmenopausal women.
- Research is needed to evaluate the role of social factors, such as social support, cultural transitions, SES, work stress, multiple concurrent life roles (e.g., mother, wage earner, primary caregiver to aged parents) and the frequency and/or intensity of life stresses in CVD risk and recovery from CVD events, including ethnic and SES differences, on the importance of these factors.
- Studies should evaluate strategies for promoting long-term behavioral changes, including strategies to promote treatment compliance, for reduction of primary and secondary CVD risk and promotion of quality of life in women.

### ***Exercise***

- Research is needed to investigate the importance of sedentary habits or exercise in the prevention of CHD and in recovery from CHD events in women. This should include studies of the interaction of exercise with other risk factors and the mechanisms by which these occur. Special emphasis should be given to older women.
- Investigations should evaluate the effects of exercise on physiological factors that are known or suspected to contribute to female protection from CVD, such as ovarian function, estrogen metabolism, and estrogen action on the artery wall.
- Research should determine the variables that influence the adoption of an active lifestyle among women and develop strategies to increase activity in various age and ethnic groups of women.

## **Obesity**

Obesity is a major problem for women in the United States, especially among minority women and those in lower socioeconomic classes. Moreover, the prevalence of obesity is increasing, as is the number of children and adolescents who are obese. Among women ages 45 to 65, 30 percent of whites and 60 percent of Blacks are obese. Obesity increases the risk of hypertension threefold, the risk of diabetes threefold, and the risk of hypercholesterolemia 1.5-fold. The psychological consequences of obesity are also profound. It has become increasingly apparent that distribution of body fat markedly influences the risks associated with obesity: women with upper-body-fat obesity (i.e., abdominal obesity) have a much greater risk of diabetes, CHD, and all-cause mortality than equally overweight women with lower-body-fat obesity. Finally, major weight gain during adulthood occurs far more frequently in women than in men and leads to increased upper-body-fat distribution, elevated insulin levels, and increased risk of CHD.

- Studies should evaluate the relationship between intra-abdominal fat and CVD risk in premenopausal and postmenopausal females. These investigations should address differences in estrogen metabolism.
- Research is necessary to investigate the effects of exercise, weight loss, and/or exogenous hormone therapy (e.g., contraceptive steroids and estrogen replacement therapy) on fat distribution pattern and its relation to CVD risk factors in premenopausal and postmenopausal females.
- Investigation should clarify the association between regional obesity and indicators of stress in premenopausal and postmenopausal females.
- Studies ought to evaluate the relationship between body fat distribution and stress, sex steroids, and metabolic processes that influence lipid and carbohydrate metabolism.
- Studies should develop more effective strategies for the prevention and treatment of obesity and should evaluate both the positive and undesired effects of such interventions.

## **Racial/Ethnic Factors**

- Studies should determine the factors that may explain the excessive burden of CHD and stroke among Black women.
- More research is needed on racial/ethnic differences on the pathophysiological mechanisms and the effect of antihypertensive therapy on mortality.
- Research should examine the mechanisms of protection against CHD in some subpopulations of diabetic women who have a low risk of CHD.
- Studies are required to determine whether differences exist in the behavioral factors that may moderate the expression of CVD in various ethnic and socioeconomic groups.
- Research is necessary to determine the variables responsible for the increase in body weight in Black women during the adolescent and young adult years and develop strategies for the treatment and prevention of obesity in Black women.

## **Nutrition**

- Studies should determine the effects of low-fat diets on changes in cardiovascular risk factors at the time of menopause, on obesity and body fat distribution, and on CHD risk. Attention should be paid to the positive effects, as well as possible undesired effects, of such diets.
- Research is needed to determine the most effective strategies for producing changes in dietary fat intake in women of various ages and of various ethnic backgrounds.

## **Special Issues**

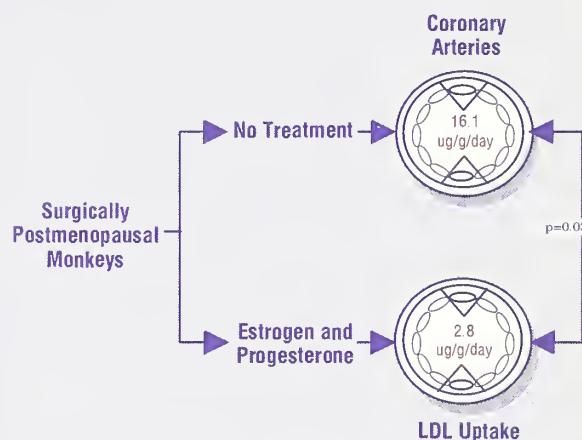
Continued study of CVD in women, while necessary, presents dilemmas for researchers. The logistics of identifying a sufficiently large cohort for statistically valid results are time-consuming. Such trials are increasingly expensive in a time of decreasing financial support, and ethical considerations of patients make some investigations impracticable or impossible. Given these problems,

the use of animal models provides a means to address further the questions pertaining to CVD in a scientifically meaningful way. Particularly useful are nonhuman primates because of their many similarities to human beings. Female cynomolgous macaque monkeys are ideal models for research on CHD. Previous research has determined that postmenopausal monkeys have a more atherogenic lipid pattern and more extensive coronary artery atherosclerosis than premenopausal monkeys. Progression of atherosclerotic disease is prevented by estrogen replacement therapy (Figure 12). The protective mechanism of estrogen replacement appears to be prevention of accumulation of LDL in the coronary arteries (Figure 13).

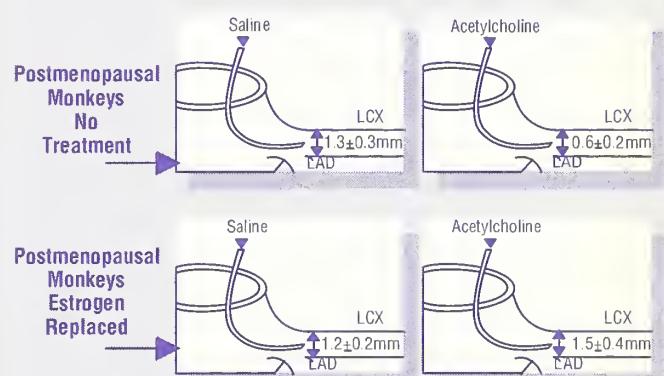
Angina pectoris associated with myocardial ischemia, but not with stenotic coronary atherosclerosis, is common in women and is probably related to coronary artery constriction. For this reason, it has been important to study the effect of estrogen deficiency on constrictor-dilator responses in coronary arteries. Using quantitative coronary angiography, dilator responses of atherosclerotic coronary arteries in surgically postmenopausal monkeys treated or not treated with parenteral estradiol have been studied (Figure 14).

- Animal models can be used to address other questions that cannot be studied in human subjects, such as estrogen effects on the artery wall, the controlled evaluation of social factors, and the systematic study of individual attributes that contribute to CVD risk. An important component of this evaluation may be an investigation of whether the effects of stress differ in perimenopausal and postmenopausal women.

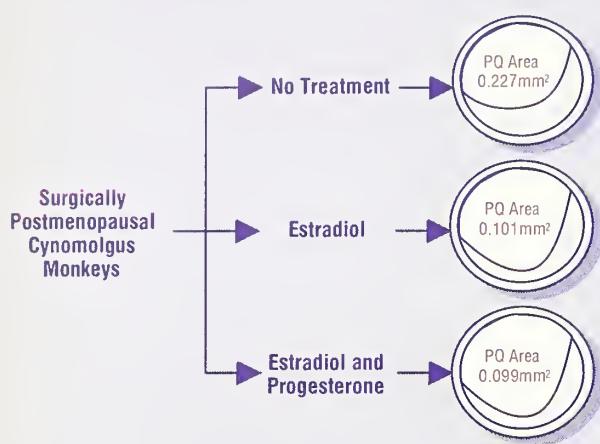
**Figure 12.  
Effect of Estrogen Plus Progesterone on Coronary Artery LDL Uptake\***



**Figure 13.  
Vasoconstriction or Vasodilation Among Surgically Postmenopausal Cynomolgus Monkeys\***



**Figure 14.**  
**Coronary Artery Atherosclerosis of Surgically Postmenopausal Monkeys\***



\*Modified from Adams MR, Kaplan JR, Manuck SB, et al. *Arteriosclerosis* 10: 1051-7, 1990.

- Animal models are also useful to study the effects of exercise on cardiac risk factors, coronary circulation, and electrophysiological properties in healthy atherosclerosis-prone and postinfarction states. These models should be used for study of the preventive effects of exercise on the development of CVD, the modification of ischemia and infarction, the pathophysiological effects of postinfarction rehabilitation, and evaluation of exercise effects on hormonal mechanisms known or suspected to enhance female protection from disease.

Administering estrogen has been shown to prevent paradoxical arterial constriction in response to acetylcholine, indicating that estrogen replacement protects against constriction in atherosclerotic coronary arteries.

## Reference

1. Eaker ED (ed). *Coronary heart disease in women. Proceedings of an NIH workshop*. New York: Haymarket Doyma, Inc., 1987

## MALIGNANCY

*Cochairs:*  
*Michele K. Evans, M.D.*  
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**W**hile cancer is the second leading cause of death among American women of all ages, accounting for 250,000 deaths each year, it is the leading cause of *premature* mortality. Approximately 60 percent of cancer deaths in women are accounted for by cancers of the lung (51,000), breast (44,500), colon and rectum (30,500), and reproductive system—ovarian, 12,500, cervical, 4,500, and uterine, 5,500.<sup>1</sup>

### **Major Themes**

Mortality rates for all cancer sites combined have declined somewhat since 1973 for women under age 55, in part because of major decreases in the incidence of cervical and uterine cancer. However, there has been little change in survival for older women and limited (if any) progress among the socioeconomic-ally disadvantaged populations. It is disturbing that the number of deaths from the two most common causes of cancer death in women, breast and lung cancer, are increasing in frequency. Moreover, mortality from these cancers, particularly lung cancer, is likely to increase substantially over the next decade.

Because the largest number of cancer cases and deaths are due to cancers of the lung, breast, large

bowel, and gynecological malignancies, this discussion is focused on these types of cancers. Nevertheless, much research draws upon other areas (i.e., quality of life, psychosocial issues, sexual function, social isolation, and the quality of care given to older women). In addition, many less common cancers present important research opportunities for future investigations, which may result in greater understanding of malignant processes and ultimately lead to improved prevention, diagnosis, and treatment for more frequently occurring malignancies.

### **Malignancy: Breast Cancer**

This year, it is estimated that 44,500 women will die of breast cancer, and the incidence is increasing: from 84.8 per 100,000 in 1980 to 112.5 per 100,000 in 1987. Increases have occurred in both older and younger women. Some of this increase is due to greater use of screening mammography and, therefore, more frequent identification and reporting of new cases. Breast cancer accounts for almost one-third of all malignancies in women, and the lifetime risk for American women is now one in nine. While some mortality reduction (5.0 percent) has occurred in white females below the age of 50, this improvement has not been seen in older

women or among socioeconomically disadvantaged populations, especially Black women.

Important opportunities for research in breast cancer exist in the areas of causation, prevention, detec-

***“Despite the prevalence of breast cancer, there is an appalling absence of information about the causes and prevention of this major killer of women.”***

*Susan Love, Director, Faulkner Breast Center, speaking for The Breast Cancer Coalition*

tion, treatment, basic science, and psychosocial factors. General linkage searches, research on possible new premalignant markers, and segregation studies of large sets of cancer families as well as the expansion of genetic studies on the Li-Fraumeni syndrome, the p53 gene, and chromosomal loci 17p and 17q, are likely to provide important new leads about familial risk and genetic predisposition. Prevention trials, including the tamoxifen trial, may provide important information on high-risk populations. Diet modification trials may become more feasible if accurate intermediate markers for dietary intake are identified.

There has already been research on the impact of screening mammography on mortality. Now, studies are needed on the use of mammography among minority, low-income women and the medically underserved as well as on barriers to use of this screening technique. However, it is important to recognize that mammography has limited usefulness, and efforts are needed to find a more specific and earlier blood or urinary marker for breast cancer. Mortality from breast cancer could be greatly reduced by developing a reliable method to detect the disease in its earliest and most curable stages. Optimum treatments with the fewest adverse effects must be identified for women whose conditions are detected at their earliest stages.

Clinical trials have led to progress in limiting surgical morbidity from breast cancer and in defining more effective adjuvant hormonal and chemotherapeutic regimens for specific patient populations. A continued search for new agents with novel targets and mechanisms should be strongly supported. Further clinical trial research should focus on adjuvant therapy trials and on autologous bone marrow transplantation and dose intensity trials for high-risk, node-positive women and for those with rapidly progressive metastatic disease. Clarification of whether the timing of surgery in relation to the menstrual cycle influences survival is also needed.

However, basic science studies constitute the only research approaches likely to make an ultimate impact on advanced metastatic breast cancer. Causative genetic elements, growth factors as targets for therapeutic intervention, tumor immunology, the biology of malignant progression, and the metastatic process appear particularly important.

Psychosocial research that focuses on the impact and amelioration of the disease is also important. Identifying populations of women who are revealed by epidemiologic or genetic research as being at increased risk poses profound psychological and ethical problems that must be addressed. Involving women in the design of clinical trials in breast cancer is likely to focus more attention on quality-of-life issues as well as increase patient entry into clinical trials and adherence to study protocols.

Exogenous hormones, including oral contraceptives and postmenopausal estrogen (with or without concomitant or sequential progestogen therapy), are used by millions of women. Thus, there is a need for detailed information on the short- and

***“Efforts should be expanded to enroll all women in mammography screening projects at appropriate ages, regardless of income.”***

*S. Eva Singletary, Assistant Professor, University of Texas, speaking for the M.D. Anderson Cancer Center*

long-term benefits and risks of taking these medications as well as information on the populations that may particularly benefit from, or be harmed by, use of these drugs.

- Epidemiologic and pharmacologic studies on the short- and long-term effects of postmenopausal hormone replacement therapy (estrogen alone and with progestins) are needed. The risks and benefits of replacement therapy need to be established for several groups. These include women at high risk for breast cancer, women with previously treated malignancies, and women who experience early menopause following treatment for premenopausal breast cancer. Other end points besides breast cancer in these studies should include endometrial cancer, thromboembolic disease, cardiac disease, and fractures.
- Basic research in the following areas is of particular importance: development of a specific and early blood or urinary marker for breast cancer detection, use of growth factors as targets for therapeutic intervention, tumor immunology, and biology of tumor progression and metastasis.
- Genetic studies should include: (1) general linkage searches (collection of family data, DNA marker analysis) for breast, ovarian, corpus, cervix, lung, and colon cancers; (2) research to test prevention interventions against new possible premalignant targets. These should be implemented first in high-risk women (i.e., in first-degree relatives of cases, in women with bilateral and unilateral breast cancer, and in women who reside in zones of excess cancer incidence and mortality); (3) for known cancer loci—breast cancer (17q + 17 p loci) and others (as recognized)—epidemiologic studies of breast cancer risk factors using gene carriers who exhibit disease versus those who do not, to clarify interactions of genetic and environmental risk factors; (4) establishment of permanent banks of both tumor and normal DNA samples from individuals with the cancers mentioned previously for use in tumor deletion studies. This might be best accomplished through a large “center” approach with collections from various large institutes that see sizeable numbers of

cases; and (5) segregation studies of large sets of cancer families with mapped susceptibilities to test for heterogeneity of cancer characteristics (penetrance, survival, etc.) by locus or by mutation. These studies should be conducted at some point in the future when several mapped susceptibilities have been recognized.

- Clinical trials research should involve women with breast cancer in the design of breast cancer clinical trials. Clinical research should focus on new agents with novel targets and mechanisms for treatment of women in the adjuvant setting as well as those with rapidly progressive metastatic disease and prospective studies addressing the timing of resection as related to menstrual cycle and subsequent outcome.
- Prevention trials should investigate the efficacy of chemoprevention agents in high-risk women (e.g., tamoxifen and micronutrients).

## Gynecologic Tumors

Together, cancers of the cervix, uterus, and ovary have an annual incidence of over 66,000 cases and result in over 22,000 deaths, according to estimates for 1991. In addition, cervical carcinoma *in situ* is diagnosed in 50,000 women each year, and lesser precancerous lesions are found in approximately 250,000 women. Each of the three cancers presents unique problems.

For cervical cancer, there is a highly effective screening test for premalignant changes of the cervix of the squamous cell type (the Papanicolaou test), but many of the underserved women in the United States do not receive appropriate screening. In addition, the large number of women with precancerous lesions (about 300,000 women) require follow-up and therapy to prevent the development of invasive cancer. This follow-up is least likely to occur for socioeconomically disadvantaged women. Uterine cancer, the most common female genital cancer, causes relatively few deaths because of successful early diagnosis. A large number of women with endometrial cancer have a long life expectancy after therapy, so the complications or side effects of therapy (such as long-term lack of hormonal replacement) are an important issue.

***"We have evidence that screening for both breast cancer and cervical cancer is worthwhile, and yet we know that women do not avail themselves of these tests. Again, there are a variety of issues there that need better research."***

*Jane Henney, Chair, Public Issues Committee, American Society of Clinical Oncology*

Finally, of all the gynecologic cancers, ovarian cancer causes the most deaths, because 65 percent of women already have advanced disease at the time of diagnosis. Some recent advances have been made in treatment of ovarian cancer, but there is no proven screening method, and little is known about precursor states.

### ***Cervical Cancer***

Through Papanicolaou test screening, premalignant cervical changes can be detected reliably and treated surgically to prevent the development of invasive cancer. The major problem with cervical cancer is the lack of information on the possible causative role and mechanisms of the human papillomavirus (HPV). Additional questions concern the relationship between the virus and the various cell types of cervical cancer, and its influence on metastatic potential.

- Research is needed to investigate HPV by focusing on its mechanisms of action and potential therapies or vaccines. Therapies are needed not only for HPV-related cancers but also for HPV condylomata and microscopic atypias. These benign lesions affect millions of women.
- Studies should be undertaken to evaluate how sexual practices of adolescent and young adult women influence the risk of cervical cancer. Studies are also needed to assess methods for healthful modification of these sexual practices.
- An important goal is to identify ways to increase utilization of existing screening methods, especially the Papanicolaou test, in underserved

populations, as well as the use of follow-up diagnosis and treatment regimens (e.g., coloscopy).

- Research to support development of new screening tests that will be more fully utilized by all women is necessary.
- Studies to define families at increased genetic risk for cervical cancer will allow linkage analysis leading to further studies of oncogenes, growth factors, and tumor suppressor genes.
- Second-level priority areas for research include: the role of vitamin deficiencies such as folic acid and retinoic acid in the development of cervical cancer; continuation of clinical trials to evaluate new drugs, drug scheduling, and biologic response modifiers; and the relationship of exogenous female hormones to cervical cancer.

### ***Uterine Cancer***

- High priorities for research include assessing the relationship between estrogen and progesterone replacement and the development of cancer and the effect of estrogen replacement on the recurrence of uterine cancer in patients who have completed therapy and are apparently free of disease.
- Research should also include linkage analysis of genetic predisposition, with subsequent identification of abnormal gene loci; an investigation of the disparity in survival of older women; and assessment of a possible risk for uterine cancer in women receiving tamoxifen.

### ***Ovarian Cancer***

At present, most ovarian cancer is already advanced at the time of initial diagnosis. The highest priority in ovarian cancer is development of screening methods to allow early diagnosis. Of equal priority is the need for basic biology studies to investigate, for example, precursor states and the mechanisms of metastasis. Genetic studies should be conducted to define high-risk families or individuals. Continued emphasis should also be placed on the development of novel monoclonal antibodies, to allow discovery of additional tumor markers, as well as to provide additional therapeutic options, especially in the area of platinum resistance and second-line therapy for recurrent disease.

Clinical trials should concentrate on developing consolidation therapies for patients rendered clinically free of disease after primary therapy because of the high recurrence rate in these women. In addition, continued investigation of new agents and new combinations of agents is warranted, given the high response rate of this cancer to chemotherapy. Finally, research on the influence of exogenous and endogenous hormones on ovarian cancer risk is indicated, and several questions are important: (1) Why have oral contraceptives been effective in decreasing the occurrence of ovarian cancer, and do the new low-dose preparations have this effect? (2) What are the effects of hormonal changes on the occurrence of the disease? (3) Is hormone replacement therapy associated with an increased recurrence rate of uterine cancer or decreased response to therapy?

- Evaluations should be undertaken of screening techniques (CA-125, vaginal ultrasound, and pelvic examination).

The Gynecologic Oncology Group, a National Cancer Institute-funded cooperative research group, is the only cooperative group performing clinical trials focused exclusively on gynecologic cancers. This multidisciplinary group performs Phase I, Phase II, and Phase III trials of surgery, radiation, chemotherapy, and biologicals. In addition, its members evaluate quality-of-life issues and are cooperating in the establishment of a national ovarian tissue and serum bank for future studies. This group should be supported as a research resource for evaluating therapy of gynecologic cancer.

## **Colorectal Cancer**

Colorectal cancer will develop in an estimated 78,500 women in the United States in 1991 and will result in about 30,500 deaths. Nearly 13 percent of women's deaths from cancer are due to colorectal cancer; it is the third leading cause of cancer-related death in women. While there is little evidence for gender differences in this disease, the magnitude of the morbidity and mortality from colorectal cancer in women demands accelerated research.

It is particularly important to investigate women's knowledge, attitudes, and behavior regarding colon cancer in order to develop appropriate interventions to promote awareness of the symptoms of this condition and appropriate health practices. Educating women and their physicians, especially gynecologists, regarding the rate of occurrence of colorectal carcinoma among women remains an important part of early detection and diagnosis. Important opportunities for research in colorectal cancer include detection, prevention, early diagnosis, clinical investigation, basic science, and better understanding of the basic biology of the disease.

- Studies should identify the predisposing genetic factors and premalignant markers associated with increased risk of colorectal cancer. Studies of *p53* and the APC gene (adenomatous polyposis coli), as well as other molecular genetic markers, will continue to be high-priority initiatives.
- Investigations should focus on the influence of mucosal dysplasia and other elements that may serve to identify those patients who require more aggressive screening and on identifying new markers of preneoplastic change for use as surrogate end points in dietary and chemoprevention trials.
- Though screening for occult blood has been a useful tool in colorectal cancer, more accurate and specific broadly applicable screening methods to enhance early detection and thereby positively affect survival are required. Tests should be noninvasive or require minimal invasiveness and discomfort.
- Prevention trials should investigate the value of various interventions such as dietary, vitamin, retinoids, or other differentiating agents, in patients with polyps. Activation states or suppression of oncogenes should be evaluated, along with studies on the influence of reproductive hormones on the effectiveness of these interventions.

- Research related to therapeutic and clinical trials should include studies of drug resistance in colorectal cancer cells; clinical trials of new drugs that counteract the mechanisms of drug resistance; clinical trials of new avenues of biochemical modulation of 5-fluorouracil; and new therapeutic interventions for advanced disease, particularly for metastatic disease to the liver.

## Lung Cancer

Lung cancer, the leading cause of cancer death in women, is almost entirely due to cigarette smoking. Smoking led to 133,000 deaths in 1988, versus 30,000 in 1965. The smoking-related causes of death include heart disease; stroke; chronic obstructive pulmonary disease; and cancer of the lung, mouth, esophagus, larynx, pancreas, bladder, and kidney.

The single most striking statistic is the increase in lung cancer deaths among women. Among white women, lung cancer has surpassed breast cancer as the leading cause of cancer death. In 1991, it has been estimated that 51,000 women will die from lung cancer, compared with 44,500 from breast cancer. While the number of lung cancer deaths among men is now beginning to level off because of a more than 20-year decline in male smoking prevalence, the increase in lung cancer deaths in women is expected to continue to rise for at least 10 additional years.

For other smoking-related cancers, such as those of the head and neck, gender ratios are now diminishing. These diseases, formerly predominant among men (like lung cancer), are becoming equally common in men and women. It is also worth noting that there is an association between active and passive smoking and cervical cancer risk.

Today's woman smoker is at greater risk of dying from a smoking-related disease than her counterpart from the early 1960s because it is likely she began smoking at an earlier age, has a greater number of years of smoking in her lifetime, smokes more cigarettes per day, and inhales more deeply. Not only has the percentage of women smoking 20+ cigarettes per day increased in every age group from 45-49 to 75+; the average age at which women begin to smoke has decreased dramatically as well,

by an age-adjusted difference of 7.2 years. In fact, adolescent survey data reveal that the age of initiation is now virtually identical for males and females and that smoking prevalence is slightly higher in adolescent females and has been so for several years. While smoking prevalence has declined in men from over 50 percent in 1965 to 31.5 percent in 1987, the corresponding data for women reveal a smaller relative change. It is projected that, by 1995, the prevalence of smoking in women will exceed that in men.

In order to decrease smoking initiation and increase smoking cessation, research needs to focus on cigarette advertising, weight control, social supports, and negative affect regulation. Cigarette advertising is a particularly important stimulus to teenage smoking initiation, and advertising that encourages smoking can reinforce ambivalence a female smoker may feel about quitting when it emphasizes slenderness, beauty, sophistication, and social prowess. Of special concern is the specific targeting of advertising at women with low prevalence of smoking, such as Hispanics and Black women. Counteradvertising can play an important role in prevention.

## **Pharmacologic Effects of Nicotine**

The pharmacologic effect of nicotine—it is a stimulant that also decreases negative emotions such as depression—may be particularly important to women, especially since women have higher rates of depression and, as a group, take more mood-modifying medications than do men. Thus, many women may use cigarettes to self-medicate for their negative emotions.

- Research should examine the interactions among gender, mood modulation, and smoking patterns and their relevance to prevention and cessation interventions.

## **Weight Gain**

A recent study of weight gain in a 10-year follow-up of a national sample of individuals who successfully quit smoking showed that women consequently gained more weight than men, on average (3.8 versus 2.8 kg), and that women had a greater likelihood of gaining 13 kg or more (13.4 percent versus

9.8 percent). Part of the addictive lure of nicotine may derive from its role in body weight regulation, especially for women.

- Research should be directed at further exploring gender-related differences in the addictive properties of nicotine and the consequences of its discontinuation.

### **Social Support**

A variety of clinical and research findings suggest that social support can play a significant role in successful smoking cessation and weight loss. However, evidence has been inconsistent. Women in particular seem to benefit from social support in cessation efforts.

- Additional research on the role of social support in smoking cessation is recommended.

### **Prevention and Suggestions**

Along with recommending further study, the priorities for research outlined below highlight some of the most interesting findings to emerge with regard to adolescent and adult female smoking. Forthcoming research should encompass as many aspects of smokers' lives as possible, focusing on the many influences on behavior, initiation, maintenance, and cessation: from the individual herself to her family, peer groups, school, work site, and the community institutions in which women participate. Readiness to change is also a significant success factor: overt changes in the habit of smoking are often preceded by positive changes in attitude and behaviors. The presence of these new attitudes and behaviors may have a predictive relationship to cessation of smoking. Intervention strategies must take a woman's readiness to

change into account, along with the feasibility of helping her alter her attitude, to be expressed eventually in new behavior. Actual changes in behavior may in fact lie beyond the end point measured in many studies. The changes that have already occurred in society's norms and the ensuing gradual decline in smoking prevalence constitute a broad example of such an effect.

- All interventions need to be culturally sensitive, targeted to specific racial/ethnic and socio-economic status (SES) subgroups of women, and should address the issue of smoking intervention as it pertains to the health care system, the worksite, and the community. Interventions should also be oriented to the different phases of a woman's life cycle because there are different risk factors for relapse during different life events.
- Research on female vulnerability to smoking initiation in adolescence should address the role of advertising and counteradvertising; weight orientation; pressure from SES peers and the normative image among women; and targeted, culturally sensitive interventions. These studies should also work to reinforce the protective racial/ethnic gender roles that account for differences in smoking rates—in other words, help preserve cultural practices that discourage females from smoking, such as disapproval of smoking. Interventions should take into consideration all relevant components of the community, including the school and family, in addition to media depictions of smoking.
- Cessation efforts should consider research on female vulnerability to continued smoking and risk for postcessation relapse, weight management and prevention of weight gain, social support factors and social norms (these should be SES specific), and the reduction of depression that is associated with smoking.

Potential risk-reducing interventions, such as not taking up smoking and smoking cessation, need to be started at an early age. However, although full-scale prevention and cessation research efforts should be emphasized, it is unfortunately true that significant numbers of women who have been smoking are now likely to develop lung cancer. Therefore, efforts must also be directed at early detection of persons at high risk.

***"Women seem to have more difficulty than men in quitting smoking. Interventions designed for women will be crucial to any national smoking cessation program."***

Gwen Keita, American Psychological Association

- Research should focus on developing accurate screening methods for preclinical histologic change (e.g., sputum cytology using monoclonal antibodies) and intermediate markers to define those at high risk (e.g., debrisoquine metabolism), chemoprevention ( $\beta$ -carotene) for those at high risk, and genetic linkage studies.

## ***Special Issues***

Special attention must be focused on those female populations that, in some cases, bear a disproportionate burden of cancer incidence and mortality. These women come from the Black, Hispanic, Native American, Native Alaskan, and Native Hawaiian populations. While the incidence of breast cancer is lower among Black women than white women, the 5-year survival rates for Black women and Native American women are significantly lower than for white women.

Black, Hispanic, Native American, and Native Hawaiian women all have higher incidence and mortality rates for cervical cancer than white women. Mortality rates for uterine cancer have fallen in both white and minority women, but this decline has been smaller in minority women.

What links these Black, Hispanic, Native American, and Native Hawaiian women? Demographics indicate that poverty is the major factor in the rise in cancer incidence and mortality for certain cancers among these groups.

*"There are some very special assets to be gleaned by looking at minorities. For example, the rate of death from malignancy in Native Americans is very much lower than in the general population. What [genetic and/or behavioral factors are] protective about being a Native American?"*

*Yohanna Clevenger, President Elect, Association of American Indian Physicians*

In addition to the role that racial and ethnic background may play, there is evidence that social and economic factors are another significant factor in incidence and mortality for many cancers. The poor are more likely to have less access to health care systems, make more sacrifices to obtain health care, find educational efforts irrelevant, and ultimately develop more fatalistic outlooks regarding their disease. Poverty also is linked to more advanced stages of disease at time of diagnosis, making the chance of cure and long-term disease-free survival less likely.

- Studies should focus on improving all aspects of individual, community, and system health practices and should involve members of the target populations in their design, to ensure that the interventions will be relevant and understandable.
- To ensure culturally sensitive studies, SES and ethnicity should be recorded in all epidemiologic and clinical research.
- Culturally relevant educational materials should be developed.
- "Zones of excess cancer mortality" should be defined and delineated. Resources should be concentrated on these high-risk groups in the areas of health education, prevention, and control interventions as well as treatment, social support networks, and tobacco control. Clinical medicine and biomedical research have focused on other groups known to have a high risk for developing disease (e.g., men and cardiovascular disease); such an approach should be used for cancer in special populations of women.

In addition, those living in poverty require special outreach efforts to overcome their survival disadvantage and elevated incidence rates. This issue requires a broadly based research approach that will require not only physicians and laboratory-based investigators but experts from the social sciences as well. Coordination with multiple Federal agencies will be mandatory.

## Reference

1. Estimated new cases and deaths for 1991.  
Source: American Cancer Society. *Cancer Facts and Figures* 1991. Atlanta: American Cancer Society



## IMMUNE FUNCTION AND INFECTIOUS DISEASES

*Cochairs:*

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**M**any diseases involve apparent aberrations of immunity that lead to chronic inflammation (Table 1). Reports show that more than 1 of every 10 people has a condition related to immunologic illnesses. These immunologic disorders affect all ages among both men and women, and they often result in disability throughout life as well as a shortened life expectancy. (See also reports from NIAID Task Force on Immunology and Allergy, September 1990, and *NIAMS Report on Women's Health Issues*, February 1991.)

Several of these autoimmune diseases affect women more than men, and all of them cause increased morbidity in women, frequently during pregnancy. Autoimmune thyroid diseases (Graves' disease and Hashimoto's disease) have an incidence of 37 to 150 per 100,000 persons, with a 15:1 ratio of women to men.

Rheumatoid arthritis (RA) is a chronic polyarthritis that affects 1 percent of the population; it occurs in women three times more commonly than in men. The onset of RA can occur at any age, affecting 113 per 100,000 U.S. children under the age of 16 and, increasing with age, reaching 5 per 100

among females over age 55. RA leads to disability and a decrease in life expectancy of 3 years, comparable to that in individuals with three-vessel coronary artery disease.

In 1987, RA was responsible for an estimated 2.1 million lost workdays, 12.0 million days in bed, and 27.8 million days of restricted activity. More than 80 percent of people with RA report some limitation of activity, and more than 10 percent are unable to perform one or more activities of daily living. In 1980, the economic impact of all rheumatic diseases combined was estimated at \$21 billion.

Systemic lupus erythematosus (SLE) is an inflammatory immune disease characterized by excessive production of antibodies directed against the body's own tissues. The incidence of SLE in different U.S. studies ranges from 1.8 to 7.6 per 100,000. Women are affected nine times more frequently than men and Black women three times more than white women. Recent work has suggested that SLE is also more common in Hispanic and Asian American women than in white women. The disease affects all ages but occurs most often in

the 20- to 40-year-old age group and is associated with increased mortality (10-year survival, 60 to 80 percent) and morbidity from, for example, renal failure or thrombotic complications.

Scleroderma (systemic sclerosis) is a chronic disease of unknown cause characterized by overproduction of collagen. Women are affected four times more than men and are usually between the ages of 30 and 40 when the disease first appears. The disease results in a 45 percent survival at 7 years.

Among the other immunologic diseases that are prevalent in women and significantly affect their quality of life are diabetes mellitus (incidence:

15 per 100,000, or 6.1 million Americans) and multiple sclerosis (more than 150,000 cases diagnosed in the United States).

All of these diseases impair function, usually of the musculoskeletal system, which reduces mobility and the ability to perform self-care. Also, Graves' disease and SLE may affect cognition and affect.

Major accomplishments have been made in various areas in regard to immunologic diseases. Much work in the past has been directed toward basic research to uncover the pathogenesis of these diseases and toward therapies to intervene in the inflammatory processes responsible for the

**Table 1.  
Immunologic Diseases\***

Allergic diseases

Allergies—*insect, food, drug, environmental*

Immunologic diseases involving the respiratory system

Allergic rhinitis/hay fever  
Chronic sinusitis  
Asthma  
Hypersensitivity pneumonitis

Collagen vascular diseases

Vasculitis syndromes, including Wegener's granulomatosis  
† Systemic lupus erythematosus  
† Cutaneous lupus  
† Scleroderma  
† Rheumatoid arthritis  
Ankylosing spondylitis  
† Sjogren's syndrome  
† Panniculitis  
Dermatomyositis/polymyositis

Immune endocrinopathies

† Autoimmune-mediated thyroid disease (Hashimoto's and Graves' diseases)

Autoimmune-mediated diabetes mellitus (type I)

† Autoimmune-mediated primary adrenal insufficiency

Immunologic diseases involving the hematopoietic system

Immunodeficiency diseases  
Acquired immunodeficiency syndrome  
Autoimmune hemolytic anemia  
Idiopathic thrombocytopenic purpura  
Plasma cell disorders  
Amyloidosis

Immunologic diseases involving the nervous system

† Multiple sclerosis  
Guillain-Barre syndrome  
† Myasthenia gravis

Immunologic diseases involving other organ systems

Eczema/allergic dermatitis  
Immune complex diseases  
Immunologically mediated renal diseases

† Indicates a disproportionate effect on women.

\* Source: *Report of the NIAID Task Force on Immunology and Allergy*, Washington, D.C.: National Institutes of Health 1990; NIH pub. no. 90-2414

morbidity and mortality of these diseases. For example, in juvenile arthritis and adult RA, the inheritance of a particular histocompatibility gene has been associated with increased susceptibility to disease.

In humans, the structure of several autoantibodies and the genes that encode them have been clarified. A particular group of autoantibodies and phospholipid antibodies have been recently characterized, and the reaction between these autoantibodies and thrombotic and pregnancy complications has been identified in patients with autoimmune diseases. Also, distinctive groups of autoantibodies have been described that can be used to identify different autoimmune diseases, such as SLE, scleroderma, Sjogren's syndrome, and inflammatory myositis, and to provide an index of disease activity.

***"Sjogren's research has estimated that as many as 2 million to 4 million Americans are affected by Sjogren's syndrome. This is one of the most common autoimmune disorders and is one of the least diagnosed. . . . The female-to-male ratio of Sjogren's syndrome is nine to one."***

*Barbara Henry, President, National Sjogren's Syndrome Association*

Therapeutic regimens in RA, including new drugs and biologic interventions, are being subjected to controlled, randomized trials. In SLE, progress is being made in characterizing the genetics and pathogenesis of the disease in animal models. Clinical trials performed at the NIH have shown that immunosuppressive drugs improve outcome in Wegener's granulomatosis and SLE renal disease. The role of the immune system in infertility and increased fetal mortality is also being investigated. Educational and counseling interventions have been shown to improve health status, as well as functional status, in patients with chronic autoimmune diseases.

In the area of infectious diseases, sexually transmitted diseases (STDs) and urinary tract infections (UTIs) have the greatest impact on women's health. STDs may occur at any time during a woman's life, but they tend to peak early between the ages of 15 and 25 years. Women bear a disproportionate burden of the impact of these diseases. STDs directly impact a woman's reproductive life by causing pelvic inflammatory disease (PID), infertility, or ectopic pregnancies. Furthermore, these infections may cause adverse effects during pregnancy, including spontaneous abortions, prematurity, low birth weight, chorioamnionitis, or congenital infections resulting in fetal loss, mental retardation, or infections in the newborn. While all women are susceptible to STDs, the incidence and prevalence of these diseases are several-fold higher in minority populations, most notably among Blacks and Hispanics who reside in the inner city. Unfortunately, due to the recent epidemic of drug abuse, differences in health-seeking behavior, and weaknesses in our health infrastructure within inner cities, these populations are witnessing an unprecedented resurgence in the frequency of STDs, with enormous economic, political, and societal impact.

Each year, 6 million women in the United States acquire an STD. Two and one-half million women acquire chlamydial genital infections, and 500,000 women acquire gonorrhea. One million women in the United States are treated for PID, and at least one-fourth of these individuals suffer serious consequences, including infertility, ectopic pregnancy, and major abdominal and pelvic surgery. During the past decade, the number of cases of involuntary infertility and ectopic pregnancies has quadrupled as a result of the increasing incidence of STDs (Appendix 6, Figures 1 and 2). Currently, ectopic pregnancies are the main cause of pregnancy-related death in Black women. In addition, the number of reported syphilis cases among women in 1990 was the highest it has been in the past 40 years (Appendix 6, Figure 3). Congenital syphilis has increased 600 percent over the past 10 years; this disease results in fetal death, brain damage, and bone deformities. Over 100,000 infants die or suffer birth defects because of STDs transmitted during pregnancy or at birth. Currently,

3 million teenagers are infected with STDs each year. Nationally, 25 percent of 15-year-old women are sexually active, and the highest rates of chlamydia, gonorrhea, and HPV infections, as well as PID, occur among adolescents. Teenagers are at particularly high risk due to unique biological factors such as an immature endocrine system and behavioral factors, which include age of sexual debut and infrequent use of condoms. The costs for chlamydial and gonococcal genital infections, PID, and their sequelae is in excess of \$5 billion per year.

Viral STDs have also become major problems, especially those caused by the human immunodeficiency virus (HIV), genital herpes simplex virus (HSV), and human papillomavirus (HPV). An estimated 15 to 20 million women are chronically infected with either genital herpes and/or HPV infections, with nearly 250,000 new cases reported each year among women (Appendix 6, Figure 4). In addition to causing symptomatic disease, HPV frequently causes chronic asymptomatic infection, which is associated with the development of cervical carcinoma.

Over 19,000 cases of AIDS in women have been reported to CDC, and an estimated 200,000 women may be infected with HIV. In 1990 the largest proportional increase in AIDS cases occurred among women, Blacks, Hispanics, and persons exposed to HIV through heterosexual contact (Appendix 6, Figure 5). As a result of perinatal transmission, AIDS is the leading cause of death among Hispanic children and the second

leading cause of death for Black children in the United States. Acquisition and transmission of HIV is facilitated by other STDs, including gonorrhea, chlamydia, syphilis, and HSV. (See Appendix 6, Recommendations for Research on Women and HIV Infection.)

Over 7 million episodes of acute bacterial UTIs occur in young women between the ages of 20 and 40. The female-to-male ratio of UTIs is 30 to 1, and as many as 6 percent of women develop a UTI each year. Approximately 250,000 cases result in acute pyelonephritis and septicemia, and 20 to 25 percent develop frequent recurrent infections; 20 percent of all medical prescriptions are for the treatment of UTIs. These infections result in considerable morbidity and time lost from work. After menopause, asymptomatic bacteriuria and symptomatic UTIs become exceedingly common, particularly among women hospitalized or institutionalized in nursing homes. Management of these infections costs well over \$1 billion per year.

Major advances have been made in our knowledge of the epidemiology of STDs, including HIV infection. Factors contributing to the recent epidemic of STDs among women are complex and appear to involve the interaction of several variables, including socioeconomic class, exchange of sexual services for drugs, health-care-seeking behavior, changes in population demographics, younger age of sexual debut, and residence in areas of high disease prevalence. The increasing STD rate has important implications. Increases in heterosexual adult STDs indicate that there will be similar trends in congenital STDs. Community health education messages—generated by concerns about HIV to reduce risky sexual behavior—have not yet permeated minority heterosexual populations. And because of the association of both genital ulcer disease and genital nonulcerative diseases with HIV transmission, control of STDs could further reduce HIV spread in this population.

***"In reference to HIV, we urgently need research on case definition in women, progression of disease, treatment trials, and prevention. Obviously, this is a matter of life and death."***

—Anke Ehrhardt, Professor and Director, HIV Center for Clinical and Behavioral Studies, Columbia University, New York State Psychiatric Institute

Utilizing new types of molecular probes and monoclonal antibodies, improved diagnostic methods have been developed that permit the early detection of STDs. The recommendation that asymptomatic

women undergo routine screening with these newer diagnostic tools has led to increased detection and treatment of asymptomatic infections, thus the further development of complications and sequelae has been avoided.

Studies delineating the pathogenesis of the microbial agents responsible for these infections have provided a better understanding of the factors responsible for the induction of the disease process. In some cases, studies have identified the molecular basis of microbial attachment to mucosal surfaces and the subsequent immune response that results in both inflammation and resistance to further infection. The structural components of these organisms have been intensively analyzed and dissected, providing information for a rational approach to vaccine development that can be utilized to prevent further infections. Potential vaccines are being developed and are in early stages of testing for gonorrhea, chlamydia, herpes, and HIV.

Antiviral drugs have been developed specifically for the treatment of herpes, HPV, cytomegalovirus, and HIV. These drugs have significantly decreased morbidity and, in the case of herpes, have decreased recurrence rates.

Molecular studies have delineated the mechanisms of antimicrobial resistance, an area of growing importance with the increasing spread of antibiotic-resistant *Neisseria gonorrhoeae*, acyclovir-resistant herpes, and AZT-resistant HIV.

## **Major Themes**

Today, there is no cure for most of the immunologic diseases noted above, nor do we know their causes. Understanding the etiology of these diseases is, therefore, a top priority. The development of successful treatment and prevention in the long term will depend on this understanding. Because of the predominance of immunologic diseases among women of childbearing years, special attention needs to be given to the interaction between these diseases and pregnancy. The relationship between socioeconomic status, cultural background, and severity of disease also needs to be further explored. Treatment is available for most of these diseases,

but it often results in additional morbidity. For this reason, more specific biologic interventions need to be developed. All study designs should reflect the incidence and prevalence of disease among women, including minority women.

For STDs and HIV, multidisciplinary approaches to research should be encouraged, since they provide a broad range of expertise that can contribute synergistically to the design and conduct of STD research. Closer collaborations should be fostered among immunologists, microbiologists, protein chemists, pathologists, epidemiologists, behavioral scientists, clinicians, and others.

Further, the recommendations for research on women and HIV infection from the National Conference on Women and HIV Infection are strongly endorsed. Issues of immediate concern in this area of research are listed below and given priority due to the magnitude of this epidemic and the mortality associated with this disease. Furthermore, the example of a national conference addressing a single medical area as it affects women's health, with the development of recommendations, is commended and should be repeated for other priority research areas (see Appendix 6).

## ***Key Issues/Research Recommendations***

### **Immunologic Diseases**

#### ***Etiology***

- Research initiatives should be developed to elucidate the etiology of immune diseases, including the role of infectious agents, the major histocompatibility complex (MHC) and complement genotype, T-cell receptors, environmental triggers, and other genetic loci linked or unlinked to the MHC (e.g., the human homologue of IDD-1), so that specific therapies can be brought to clinical trials as early as possible.

#### ***Pathogenesis***

- Studies are needed to understand the immunologic rules that govern tolerance and nontolerance and the distinction of self from non-self. These

mechanisms should be examined systemically and, in particular, at actual disease sites (target organs, such as joints, thyroid, ovary), with emphasis on gender (hormonal and sex organ specificity) differences.

- Research should explore more fully the mechanisms involved in the processing and presentation of autoantigens and foreign antigens and the difference between autoantigens and foreign antigens, as well as how these differences may relate to gender influences.
- Investigations should seek to define the role of cytokines in the potentiation and amplification of immunologic reactions and diseases, in terms of both their effect on cell-cell interactions (i.e., cell-mediated immune and humoral response) and on the extracellular matrix.
- The structure and function of the extracellular matrix should be explored, along with the relationship between immune cells and this matrix as it is mediated by adhesion receptors (e.g., ICAM-1).
- Studies should investigate the relationship between pregnancy and immunologic processes using modern immunologic techniques, including studies of immunology in pregnancy as a normal physiological process to shed light on mechanisms related to tolerance and recognition of self, and studies to explain the immunosuppression observed in pregnant women, which may result in susceptibility to infection. These findings may shed light on such conditions as pre-eclampsia, preterm birth, early ovarian failure, and spontaneous abortion, as well as tumor development and host responses to organ transplantation.
- Research is needed to explore the role of auto-antibodies in the pathogenesis of autoimmune diseases (e.g., the role of antiphospholipid antibodies on vascular endothelium and coagulation and the pathogenesis of the neonatal lupus syndrome).

### **Epidemiology/Natural History**

- Research should explore, using population-based and cohort (longitudinal) studies, the interrelationship of the immune system and pregnancy, including antiphospholipid antibodies and their association with early fetal loss and intrauterine growth retardation, pre-eclampsia, and habitual abortion.
- Multicenter data bases of patients with immunologic diseases need to be established and supported to facilitate basic epidemiologic and clinical therapeutic research.
- Studies should determine the incidence, prevalence, and morbidity (severity) of immunologic diseases (i.e., SLE) in women of different racial and ethnic groups (Blacks, Asian Americans, Hispanics, and Native Americans) and differences in the incidence, prevalence, and morbidity of these diseases in women versus men.
- Research is needed to understand the natural history and evolution of immunologic diseases. Studies should determine whether the natural history of these diseases is changing. For example, does prolonged survival in SLE patients lead to better recognition of complications of disease and its therapy? Are there changes in incidence and severity of RA, and are these modified by oral contraceptive use? Also, more studies are needed to quantify and describe the spectrum of disability (health status) that results from immunologic diseases and its modification throughout the life span. Issues of measurement of disability must be addressed in women versus men and in women of different racial, ethnic, and socioeconomic groups.

### **Clinical Intervention**

- Studies are needed to develop new therapeutic agents, based on findings from basic research, and specifically designed for women (e.g., combination drug therapies, biologic interventions such as T-cell receptor blockage, peptides, and experimental T-lymphocyte vaccines for autoimmune disease).

- New methods are necessary to deliver pharmacological agents and to determine the specific parameters of drug pharmacokinetics, giving special attention to gender, age, and menstrual cycle. Better methods are also needed to evaluate drug efficacy and to monitor drug toxicities, especially in patients who require corticosteroid and immune suppressive treatments. Studies are necessary to identify patients at high risk for drug toxicity, with attention to long-term effects (e.g., infertility, osteoporosis, coronary artery disease, and fetal outcome).
- Research is needed to explore the management of immunologic diseases during pregnancy (e.g., in asthma patients, patients with connective tissue diseases, transplant recipients, leukemias, and individuals with a primary immunodeficiency).
- Scientific studies should investigate the influence of nonpharmacologic treatments on immunologic status (e.g., diet manipulation in pregnant women) and their effects on subsequent allergic states in offspring, immunogenicity of surgical implants, exercise, ultrasound, and physical modalities used to treat acute and chronic pain.
- Studies are needed to determine the efficacy and mechanisms of action of nonpharmacologic, culturally sensitive treatments in preventing morbidity and reducing functional disability (e.g., rehabilitation modalities, including physical rehabilitation techniques such as supportive devices and sociobehavioral interventions, including group support and self-efficacy programs).

#### ***Behavioral/Educational Strategies***

- Studies should describe and define the relationships between SES and disease onset and severity and explore the possibility of causal relationships between educational status/income/vocation and morbidity and mortality.
- New culturally and gender-sensitive educational and behavioral interventions should be developed to reduce the morbidity and mortality associated with immunologic disease and its treatments.

## **Infectious Diseases**

### ***Basic Research***

- Studies characterizing the mucosal immune system of the genital tract in healthy women and its role in susceptibility to infection and/or the prevention of infection are urgently needed. Research on the function of the mucosal immune system—specifically, antigen-processing, humoral, and cellular immune responses, and the effects of hormones on these responses—should be performed.
- The immune response is important to the clinical consequences of many STDs, including HIV (immunosuppression) and chlamydia (autoimmune responses as a consequence of exposure to shared or common antigens). Mechanisms of these phenomena need to be better understood; this knowledge may lead to better therapy and vaccine development.
- Basic research on the microbiology, immunology, and pathogenesis of microbial pathogens is essential to the eventual design and development of effective vaccines against STDs/HIV. Prototypes of vaccine for use in the prevention of *N. gonorrhoeae*, *C. trachomatis*, HIV, and HSV are underway and should be intensified with additional resources. Continued research is urgently needed on the function, structure, pathogenic roles, and immunogenicity of multiple microbial antigens, using the full array of available research tools. Mapping of the epitopes involved in protective mucosal immune responses is essential to vaccine development.
- Understanding the nature of pathogen-cell interactions, especially microbial attachment, entry, and persistence, is essential to the development of effective strategies for interrupting transmission. In addition, factors and mechanisms of host/parasite interactions, latency, virulence, and carcinogenesis (in the case of HPV) need to be examined.
- Clarification of the bacterial determinants—including microbial virulence factors at the molecular and biochemical level—that facilitate the development of PID and its sequelae is

needed. Animal models should be developed to further explore the relationship between lower and upper genital tract infections, including the mechanisms by which pathogens invade and induce acute and chronic inflammatory changes in the endometrial cavity and the Fallopian tubes.

- Research is necessary to study the immunogenicity and safety of vaccines given during pregnancy and their immunologic effects on the neonate. In addition, immunologic studies should be directed at the protective immune responses during breast-feeding to identify the components in breast milk primarily responsible for inhibition of specific pathogens. Similarly, studies on the role that breast-feeding plays in the transmission of certain infections such as HIV, as well as the immunologic consequences of pregnancy and lactation on the progression of HIV infection, should be undertaken.
- The microbial and host (anatomic, hormonal, and immunologic) factors responsible for the heightened susceptibility to UTIs among women need to be better defined.

### **Epidemiology**

- Prospective cohorts of adult and adolescent women should be established to determine the natural history and clinical presentation of STD/HIV infections in women. Factors that affect the progression to AIDS among HIV-infected women should be identified, and the types of opportunistic infections that occur in women should be more intensively studied. Clinical, virologic, and immunologic markers of disease progression should be evaluated in regard to the female-specific end points of disease progression.
- To better understand, prevent, and treat HIV infection in women, studies need to address the frequency of, and factors responsible for, transmission of HIV to women, with specific focus on STDs, stage of disease, immunologic state, pregnancy, hormonal influence, and age. Studies on the frequency and factors responsible for transmission of HIV from mother to child should be continued, and therapy for preventing transmission should be evaluated.

- Detailed studies on the interrelationships of STD infections and HIV infection should be initiated. These studies should focus on how the facilitation of HIV by concomitant transmission of syphilis, chancroid, and other STDs may increase the incidence of HIV and also investigate whether certain infections may be opportunistic consequences of HIV disease (e.g., HPV and cervical disease). Studies should address the effect of HIV infections on diagnosis of STDs and their response to therapy, as well as the effect of concurrent STDs on progression of HIV.
- Factors and mechanisms that alter the risk of disease progression are poorly defined, for example, HPV infection and its association with premalignant and malignant lesions of the genital tract. Epidemiologic studies are necessary to further define the factors that are necessary for initiation versus potentiation of atypical cell growth. Natural history studies of HPV infection and the influence of the immune system are critically important in attempts to prevent the development of cervical cancer.
- The natural history of various types of PID, particularly atypical or subclinical PID, is in need of careful study. The specific risk factors and risk markers for the development of PID, tubal factor infertility, and ectopic pregnancy need to be investigated.
- Future research should characterize the role of STDs in adverse outcomes of pregnancy. Factors such as the infecting pathogen, the stage of gestation during which infection occurs, chronicity of infection, and behavioral patterns such as drug abuse should be studied. Organisms should be specifically examined for virulence factors and other markers associated with specific patterns of fetal or neonatal morbidity.

### **Clinical/Therapeutic**

- Vaccine trials designed to prevent infections caused by STDs/HIV, as well as therapeutic practices to prevent adverse consequences or progression of these infections, are of highest priority and should be strongly supported with additional resources.

- Utilizing advances in molecular biology, more sensitive diagnostic assays for improved detection of STDs should be developed. These assays should be cost-effective and practical for rapid diagnosis in order to effect immediate therapy.
- Therapeutic studies of STDs that specifically address efficacy, safety, compliance, and cost should be encouraged. The most pressing research challenge in STD treatment lies in the development of curative antiviral agents for infectious agents such as for HPV, HSV, and HIV. Institution of novel therapeutic regimens for PID using new antimicrobials and anti-inflammatory agents should be assessed in terms of clinical response and decreased sequelae.
- Protocols for the safety and efficacy of experimental antiviral drugs, documents required for drug licensure, and protocols for experimental vaccine trials should be developed that include practical guidelines for use in pregnancy. Specifically, therapeutic agents against HIV and treatment of opportunistic infections and other STDs should be evaluated in both pregnant and nonpregnant women.
- Community research programs for the treatment of STDs/HIV should be expanded, and mechanisms to increase access to care, particularly among low-income women and adolescents, should be identified. These programs should include the development of cost-effective models of HIV care in community sites such as methadone and drug treatment units, STD clinics, and family planning units.
- Better barrier/contraceptive methods and viricides that are effective, safe, inexpensive, easy to use, and controlled by women must be developed and studied.
- Diagnostic algorithms for PID should be developed based on epidemiologic, clinical, and simple laboratory data that can be evaluated against clearly defined gold standards such as laparoscopy and endometrial biopsy.
- Noninvasive diagnostic techniques for typical and atypical PID also warrant development and study.
- HIV, tuberculosis, drug-resistant tuberculosis, syphilis, and intravenous drug use are strongly associated; research should focus on development of new drug therapies, their safety in pregnancy, and possible drug interactions with methadone.
- Studies should seek to define the gender- and age-specific characteristics that predispose the adolescent female to STD infections and complications, especially PID and AIDS. Studies should compare the impact of specific STD infections, especially chlamydia, HPV, and HIV infection, on the immature and mature endocervix.
- Specific research should be directed to the development of better diagnostic and therapeutic approaches to UTIs, including interstitial cystitis and culture-negative urethritis.

## **Behavior/Education**

Most sexually transmitted infections are acquired because of sexual behaviors. Our knowledge of sexual behaviors in the various racial, ethnic, and sociocultural groups is severely limited. The recent administrative cancellation of an approved and funded study of adolescent sexual behaviors in this country has caused concern over the priority of these studies and the effectiveness of the scientific review process. Without knowledge of sexual attitudes, beliefs, and behaviors and of individual and group forces that influence these behaviors, how can we rationally design and implement effective programs that reduce risky behaviors?

- Collaborative efforts among epidemiologists, medical anthropologists, behavior scientists, educators, and others are necessary to acquire a data base on sexual behaviors and to formulate programs that lead to reduced rates of genital tract infection.
- A specific behavioral research agenda in STD prevention is needed. Behavioral studies should identify the type and prevalence of behaviors that put individuals at risk for transmission or progression of an STD/HIV. Also required are determinations of population rates for STDs/HIV and behavioral and epidemiologic research that assesses the determinants of sexual transmission, including demographic, gender-specific, sociocultural, and contraceptive factors.

- Studies should examine whether there is a biologic basis in adolescents for an association among the timing of pubertal maturation, the onset of sexual debut, and initiation of drug use. The unique characteristics of adolescent sexual behavior and drug use should be defined.
- Research on beliefs and attitudes of women concerning contraception, receipt of experimental and other therapies during pregnancy, and on participation in clinical trials during this period should be conducted.
- Behavioral research should address health-promoting attitudes, knowledge and behavior assessment, compliance, patterns of health-seeking behavior, and relapse/recidivism issues. It is essential that all interventions have a comprehensive evaluation component that assesses the bidirectional impact of the intervention at individual, group, community, and system levels.
- With increasing use of contraception administered via intramuscular depot, the hormonal and behavioral influences on STD acquisition and disease manifestation deserve careful and intensive study.

## Urologic Diseases of Women

Urological disorders in women constitute a national health care burden of great magnitude in pain, suffering, and economic impact. Emphasis should be placed on the study of urinary tract infection, interstitial cystitis, and urinary incontinence.

### Urinary Tract Infection

Infections of the urinary tract are particularly common in women and result in considerable morbidity and time lost from work. Costs for treatment and lost wages exceed \$1 billion annually.

UTIs account for 8 million office visits annually and affect one woman in five during her lifetime. Twenty-five percent of women with infection develop frequent recurrent infections, and approximately 250,000 cases each year result in acute pyelonephritis and septicemia.

***"The female-to-male ratio of the incidence of urinary tract infections is 30 to 1. The rate of infection in the female population in the United States is approximately 6 percent per year."***

Gail Cassell, Chairman, Committee on Medical Biology and Immunology, American Society for Microbiology

- Emphasis should be placed on researching the mucosal immune system of the human female genital tract and its role in prevention and/or its susceptibility to infection.
- Research on function of the mucosal immune system, specifically, antigen-processing, humoral, and cellular responses and the effects of hormones on these responses, should be pursued.

### Interstitial Cystitis

Interstitial cystitis (IC) is an extremely painful and debilitating inflammatory disease of the urinary bladder. It occurs almost solely in women, and is estimated to affect as many as 450,000 individuals in the United States. The etiology is unknown, and there is no effective treatment.

The economic impact, derived from medical expenses for treatment and lost wages due to disability, is estimated to be \$1.7 billion per year.

***"Only in the last decade did the standard urological textbook, Campbell's Urology, stop describing [interstitial cystitis] as a hysterical female condition . . ."***

Vicki Ratner, President and Founder, Interstitial Cystitis Foundation

- Research should be directed toward determining the pathogenesis and ultimate etiology of IC-isolating markers to better define and diagnose the disease, develop more specific diagnostic tests, and find effective treatments. Emphasis should be placed on research investigating infection (with fastidious organisms) as a possible etiology of IC in view of recent findings on *Helicobacter* and its role in gastritis.
- In addition, funding must be directed toward the education of physicians, given the average length of time—2 to 5 years—it currently takes to get a diagnosis of IC. It is also important that awareness of IC be promoted from within the scientific community in order to attract new researchers in urology as well as in related fields.

### **Urinary Incontinence**

Urinary incontinence affects approximately 10 million adult Americans, 85 percent of whom are women. Fifteen to 30 percent of community-dwelling older residents, and at least 50 percent of all nursing home residents, are incontinent. Costs in managing urinary incontinence are estimated at \$10.3 billion annually. With proper diagnosis and appropriate treatment, 30 to 50 percent of incontinent women can be cured or their condition significantly improved.

- Research should focus on determining the causes of incontinence, identifying high-risk patients, developing prevention strategies, and developing improved surgical and nonsurgical treatments.

### **Special Issues**

Once a woman is diagnosed with an STD such as HIV infection, she encounters numerous barriers to enrolling in clinical studies, particularly clinical trials for experimental drugs. These hindrances include criteria for inclusion such as a minimum weight requirement, no allowance for gender-specific lab values such as lower hemoglobin counts, a prohibition against inclusion of pregnant or nursing women, and a requirement for effective contraception among women enrolled in the trials. Special problems related to child care, transportation, substitute caretakers, access to routine

medical care, abortion facilities, and drug treatment programs are problems that confront many HIV-infected women. Research and public policy programs must address these issues aggressively.

Finally, new animal models (e.g., nonhuman primates and mice) that mimic the condition of the autoimmune diseases are needed, especially for SLE and RA.

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## APPENDICES



# APPENDIX 1

## ***Women's Health Initiative: Clinical Trials and Observational Study***

### ***Introduction***

The health of women has extraordinary medical, social, and economic importance, as well as the personal interest of women in making choices of healthy behaviors. However, too little research has focused on health issues unique to, or more common for, women. This is especially the case for studies of chronic diseases in mature women. These conditions, cardiovascular disease, cancer, and osteoporosis, are the leading causes of mortality, morbidity, and declining quality of life. Recognizing this, the Director of the National Institutes of Health (NIH), Dr. Bernadine Healy, announced the development of a research project to address these issues. These studies have been titled the Women's Health Initiative (WHI). Scientific staff from 10 Institutes of NIH have joined together to plan this initiative that is coordinated by the Office of Disease Prevention and the Office of Research on Women's Health. After presentation of an initial concept in May 1991, the executive committee, made up of Institute directors, directed that a detailed plan be developed and reviewed. As issues arose, experts were brought in to address specific questions. Because the Women's Health Initiative is a large and important study, we obtained comments and review on a prospectus of this plan by interested groups outside of NIH at public hearings held on October 28 and 29, 1991. The comments received at that meeting were carefully considered, and wherever

possible, recommendations have been incorporated in the planning of the WHI. Following further internal reviews, a series of requests for proposals will be developed and issued for response by the research community by June 30, 1992. The proposed plan presented in this document is not a request for proposals and is not a final protocol; these are subsequent steps that will follow this review. We have attempted in this document to provide sufficient detail to permit concept review of the Clinical Trial and Observational Study.

### ***Overview***

The Women's Health Initiative has two main goals. The first is to evaluate preventive approaches to cancer, cardiovascular disease, and osteoporotic fractures. These approaches are hormone replacement therapy, low-fat dietary pattern, and calcium and vitamin D supplementation, and these will be tested in a large clinical trial (the Clinical Trial component). The screening and recruitment of large numbers of women also affords a unique opportunity for observational studies of disease predictors (the Observational Study component). The second goal is to evaluate strategies to achieve healthful behaviors that have established value, including smoking prevention and cessation, improved dietary pattern, achievement and maintenance of optimal weight, increased physical activity, and early cancer detection. This goal is addressed by a community trial that will organize community resources to improve adoption of

healthy behaviors and to remove barriers to their adoption (the Community Trial component). The outcome of these studies will enable scientifically validated advice to be given to women, their physicians, and public health workers about healthy behaviors and treatments and a process that supports adoption of healthy behaviors. The current document addresses only the Clinical Trial and Observational Study components of the WHI.

The Clinical Trial and Observational Study will direct particular attention to recruitment and study of minorities and medically underserved segments of the population in a culturally sensitive manner. The information derived from these studies will be relevant to all women regardless of racial, cultural, or economic status.

The treatments to be tested in the Clinical Trial and the Observational Study are integrated into a single initiative to improve scientific and fiscal efficiency. The plans presented in this document have been developed in sufficient detail to permit estimates of size, cost, and statistical power to answer the questions. However, this does not constitute a final protocol. The final protocol will be developed collaboratively by the coordinating center, vanguard clinical centers, and NIH staff.

The plans for the component parts of the Clinical Trial and Observational Study are described in succeeding sections. These sections are separated into background, description of design, and expected results. The Community Trial Component will be described in a separate document and will form a separate set of contractual studies.

### ***Clinical Trial of Hormone Replacement Therapy, Low-Fat Dietary Pattern, and Calcium/Vitamin D Supplementation***

The trial is designed to address the major causes of mortality and morbidity in postmenopausal women, namely coronary heart disease, breast and colorectal cancer, and osteoporotic fractures. Cardiovascular disease is the most common cause of mortality in older women, accounting for 29 to

48 percent of all deaths in the age range 50 to 79. Both absolute rates and proportional mortalities from these causes increase steeply with age. Among the cancers, breast cancer is the second most common cause of death. Even though rates increase with age, the proportional mortality from breast cancer is higher at younger ages. Colorectal cancer is the third most common cause of death among the cancers (after lung and breast) and the second most common incident cancer. Rates of colorectal cancer increase with age. Fractures account for considerable morbidity, fragility, and loss of independence. Annual fracture rates also increase with age.

The goals of the treatments to be tested are to reduce the incidence of disease and subsequent morbidity and mortality, and these reductions should translate into substantial improvements in the quality of life of postmenopausal women.

Multiple end points will be studied to gauge the effect of the proposed interventions on overall health. These include coronary heart disease, breast cancer, colorectal cancer, and osteoporotic fractures. Each of the treatments is expected to influence a number of end points. Thus, hormone replacement therapy may benefit both coronary heart disease and fractures; low-fat dietary pattern may benefit breast and colorectal cancers and coronary heart disease; and calcium supplementation may benefit fractures and colorectal cancers. It is important to measure the total benefit to the individual and not to focus on benefits to a single condition. When women and their health providers decide on an approach, they will want to know the total benefits and risks.

The trial also will address unresolved issues relating to possible adverse effects, such as an increase in breast cancer or endometrial cancer on hormone replacement therapy, and will examine an increase of renal calculi on calcium supplementation. Importantly, the measurement of a broad range of treatment outcomes will permit determination of benefit and risk for treatments.

The trial is a controlled clinical trial of preventive treatments in women ages 50 to 79. There are three main components: hormonal replacement therapy, low-fat dietary pattern, and calcium/vitamin D

supplementation. The sample size requirements are large enough to test each treatment with confidence. The treatments will be tested in a partial  $3 \times 2 \times 2$  factorial design in order to keep the total number of participants manageable.

## Hormone Replacement Therapy

### Hormone Replacement and Cardiovascular Disease

Hormone replacement therapy in postmenopausal women may prevent coronary heart disease and osteoporosis. The incidence of cardiovascular disease (principally coronary heart disease and stroke) increases substantially in the decades following menopause. Both the rates and the proportion of all deaths from cardiovascular disease increase with age. Approximately 500,000 women (and about the same number of men) die annually from cardiovascular disease; almost all of these deaths occur in the postmenopausal age groups, and it is the major cause of death in postmenopausal women.

The decrease in the circulating levels of estrogens following menopause is thought to contribute to the increased rates of coronary heart disease. In premenopausal women, estrogens may retard the development of atherosclerosis and protect against coronary heart disease through favorable effects on lipoprotein metabolism and possibly on other factors such as fibrinogen, blood pressure, and insulin levels. Reduction in estrogen levels may partly account for the observation that low-density lipoprotein (LDL)-cholesterol levels increase during the transition into menopause and continue to increase for some 10 to 15 years thereafter. There also may be a slight decrease in high-density lipoprotein (HDL)-cholesterol levels during menopause. Estrogen replacement therapy decreases LDL-cholesterol levels by about 15 percent and increases HDL-cholesterol levels by a similar amount.

A reduced risk of developing coronary heart disease for women taking estrogen replacement has been found in published studies. These reductions were observed for nonfatal as well as fatal coro-

nary heart disease and cardiovascular disease. In several of the studies, risk reduction appeared to be even more substantial in women with existing vascular disease. The benefits appear to increase with prolonged and current use compared with previous use. It is not known whether obese women, who tend to have higher levels of endogenous estrone, will benefit from hormone replacement therapy to the same extent as lean women.

However, it is not clear whether the apparent benefits of estrogen replacement from these observational data are largely due to self-selection by which healthier individuals are prescribed estrogen replacement, other selection biases in inclusion of subjects, or reporting of study results. Such biases may not only exaggerate the apparent benefit, but may also underestimate the magnitude of adverse effects. Studies that have attempted to control for confounders have generally concluded that hormone replacement exerts an independent effect; however, it is almost impossible to control for these (and other possibly unrecognized) sources of bias adequately in observational studies. The observational studies do not provide experience or data with estrogen plus a progestational agent, the most common approach to postmenopausal hormone replacement currently in use. Therefore, although the observational studies provide a basis for developing a hypothesis that hormone replacement therapy may reduce the risk of coronary heart disease, *an hypothesis for protection of estrogen or estrogen plus a progestin can only be tested reliably by a well-designed randomized trial.*

### Hormone Replacement and Bone Fractures

Although fractures are not a major overall cause of death, those women who are hospitalized for hip fractures have a mortality rate as high as 30 percent from complications such as thromboembolism, fat embolism, and pneumonia and from surgical deaths. Fractures are common at older ages and are a major cause of morbidity and loss of mobility. It has been estimated that a 50-year-old woman has a 12- to 15-percent chance of being hospitalized for hip fracture during her remaining

lifetime. Fracture rates increase markedly with age, being negligible at ages below 55 years. At any age, the rates in women are twice as high as those in men.

Postmenopausal women lose about one-third of their cortical bone and one-half of their trabecular bone. Risk factors relating to bone loss include female sex, increasing age, Caucasian race, oophorectomy, early menopause, prolonged immobility, and insufficient dietary calcium. Protective factors include estrogen replacement therapy, obesity, and physical activity.

The major effect of estrogens on bone mass appears to be in the years immediately following menopause, although the peak rate of fractures occurs some decades later. Nevertheless, at any age, estrogens may have the potential to prevent further loss of bone, suggesting that even at advanced ages, women receiving estrogens may benefit compared with those who do not. Observational studies indicate that women taking estrogens have greater bone mass and a lower fracture rate. However, the effectiveness of estrogens in preventing fractures has not been adequately tested in a clinical trial because of the large numbers of women needed to obtain a definitive result.

## Potential Adverse Effects of Estrogen Replacement Therapy

The use of estrogen may increase the risk of endometrial and possible breast cancer and thromboembolism. The overall risk of breast cancer appears to be increased by about 7 percent, and this risk appears to be related to duration of exposure (increasing to 30 percent after 15 years), timing (higher in premenopausal women), dose (higher at doses of conjugated equine estrogens above 1.25 mg/day), type of estrogen (higher for estradiol than for conjugated equine estrogens), and family history of breast cancer (higher in women with a family history).

The relative risk for endometrial cancer incidence appears to be increased four- to tenfold over 6 years of treatment and may persist for some years following cessation of treatment. However,

the risk of death from endometrial cancer apparently is not increased. This may be because the endometrial cancers are identified early in these women who are generally under close surveillance or because the type of endometrial cancer induced by estrogen therapy is relatively non-invasive.

Because coronary disease accounts for a far larger proportion of all deaths in postmenopausal women than cancers of the breast or endometrium combined, a reduction of 45 percent in coronary deaths will numerically far exceed even substantial increases in the cancer deaths. Nevertheless, other considerations such as overall quality of life and fear of cancer will influence the acceptability of hormone replacement therapy to individual women. The addition of a progestin may reduce or eliminate the risk of endometrial cancer while the effect of progestin on breast cancer risk is uncertain. In practice, physicians are increasingly adding progestin to estrogen replacement in women who have intact uteri. It is not known whether the addition of a progestin will counteract the potential benefit of estrogen on vascular disease because there are no published epidemiologic data on this point. Progestins increase the incidence of physical side effects such as breast tenderness, bloating, edema, and abdominal cramping, and they increase the incidence of psychological side effects such as anxiety, irritability, and depression.

## Description of the Design

The clinical trial will be able to assess the overall benefit and risk of hormone replacement therapy and thereby provide information on the global impact on women's health. The proposed trial will evaluate the effects of hormone replacement therapy on coronary heart disease (the primary outcome) and fracture rates, and provide new evidence on cancers of the breast and endometrium and on quality of life. In addition, information on the possible mechanisms through which estrogens mediate their protective effect on coronary heart disease and cardiovascular disease (e.g., plasma lipids, clotting factors, blood pres-

sure, blood glucose, body fat distribution) can be obtained during the trial.

## Expected Results

The proposed clinical trial has enormous public health importance because of the common occurrence of the diseases to be studied (coronary heart disease and fractures) and the potentially large risk reductions obtainable. Even if the reductions in coronary heart disease incidence and fractures are more modest than those suggested by the observational studies, such reductions could still have a major public health impact provided that they are not offset by substantial increases in incidence of breast cancer, endometrial cancer, or thromboembolism.

## *Low-Fat Dietary Pattern*

### Dietary Modification and Cancers of the Breast and Colon

In U.S. women, breast cancer has the highest incidence and, after lung cancer, the second highest mortality. Approximately one out of every nine women will develop breast cancer during her life. In 1991, an estimated 175,000 cases of breast cancer will be diagnosed, and 44,500 deaths will occur. Breast cancer incidence rates have increased about 2 percent per year since the early 1970s, whereas mortality rates have remained fairly stable over the past 50 years.

International correlation studies show a strong positive association of per capita fat consumption with breast cancer incidence and mortality rates. Breast cancer is more common in countries with high average consumption of total and saturated fat; protein, particularly animal protein; and total calories. For example, breast cancer incidence rates are more than fivefold higher in the United States than in Japan. Persons migrating from areas with low rates of fat consumption to areas with high rates acquire the higher rates of their adopted country; for example, Japanese migrants to Hawaii and Italian migrants to Australia experience higher rates of breast cancer, suggesting

that environmental factors are of importance. Although consistent evidence from animal studies support a positive association between increased dietary fat intake and increased risk of breast cancer, analytical epidemiologic studies in individuals (case-control and cohort studies) have produced inconsistent results. This may be partly due to the known difficulty of quantifying individual dietary intake.

Colorectal cancer is the third leading cause of cancer deaths in U.S. women, and the incidence is second only to that of breast cancer. An estimated 78,500 new cases will be diagnosed in 1991, and approximately 31,000 deaths from colorectal cancer will occur.

Epidemiologic and animal studies conducted over the past few decades have established a strong link between dietary factors and colorectal cancer. Various dietary constituents have been implicated, including fat, excess calories, and reduced dietary fiber. International correlation studies show a linear relationship with total dietary fat availability and fat consumption. Studies of migrants from areas with diets low in animal fat and protein to areas with a more typical "Western" diet with high fat intakes show an increase in incidence of colorectal cancer among the migrants when compared with incidence in the country of origin (e.g., migration from Japan to Hawaii and from Italy to Australia).

In observational studies, the link between dietary fat and colorectal cancer is inconsistent. However, the large Nurses Health Study did show a positive correlation between total fat intake and colorectal cancer. Several international correlation and case-control studies have shown inverse relationships between the intake of high-fiber foods and colon cancer risk. High intake of fruits and vegetables has been consistently related to lower risk of colon cancer, whereas the consumption of cereal grain products has been either unrelated or positively associated with risk of colon cancer. The majority of analytic epidemiological studies that have had reasonable capability assessing dietary fiber have generally shown a protective effect for fiber.

## Dietary Modification and Coronary Heart Disease

The etiology of coronary heart disease has been linked to high-fat diets through international studies. Saturated fat intake as a percentage of calories correlated strongly with coronary heart disease mortality rates in the Seven Countries Study. A lifelong low-fat diet may in fact exert beneficial effects on coronary heart disease rates beyond its influence on blood cholesterol. The slope of the line relating dietary percentage of calories from saturated fat to coronary heart disease is nearly 2.5 times steeper than that for serum cholesterol and coronary heart disease. Migrant studies (e.g., Japanese migrants to Hawaii) demonstrate an important effect of saturated fat consumption on coronary heart disease rates. As in the case of cancer, and probably for the same methodologic reasons, it has been difficult to demonstrate a significant effect of saturated fat on coronary heart disease in analytic studies of individuals within populations.

## The Need for a Controlled Trial of a Low-Fat Eating Pattern

Many types of evidence bear upon the hypotheses of interest in the proposed dietary intervention trial, namely that dietary intakes of fat, grains, fruits, and vegetables are related to the incidence of breast and colorectal cancers. Considerable differences of opinion continue to exist among scientists on the "diet-cancer" hypothesis, largely because of numerous limitations and inconsistencies in the available data.

Animal experiments are important for demonstrating plausible biological mechanisms and for confirming or explaining the results of epidemiological studies, but the results cannot on their own be extrapolated to humans. If a marker for disease exists, then clinical metabolic studies may be performed to test the effect of dietary modifications on the marker. No such marker currently exists for breast or colorectal cancer.

Studies correlating international data on incidence of disease with food disappearance data

and migrant studies provide useful evidence for these hypotheses. However, this cannot be entirely relied upon because the studies do not link dietary habits with disease incidence at the individual level. They also cannot adequately control for confounding factors that may influence the disease rate.

Case-control studies overcome some of these problems but suffer from possible biases in the selection of cases and controls, differential recall of dietary intake by cases and controls, and non-differential error in the measurement of dietary intake. Prospective cohort studies avoid selection and recall biases but still rely upon food questionnaires that are known to involve substantial measurement error. These problems are compounded by the narrow range of intakes of the populations typically entering a case-control or cohort study.

## Expected Results

Definitive studies to test the effectiveness of dietary interventions to reduce cancer incidence and mortality are not available. The proposed randomized trial will have an appropriate design and will have the power to provide a definitive answer. At the same time, it will provide estimates of the effectiveness of a low-fat dietary pattern in preventing coronary heart disease as well as provide information on the effects of such a dietary pattern on serum cholesterol, blood pressure, blood glucose, and body weight. If a low-fat diet does reduce the incidence of any one of the clinical end points of cancer or coronary heart disease, the public health implications will be important because it may lead to an even greater emphasis on low-fat dietary pattern in public health recommendations and clinical practice. The credibility of such recommendations will be enhanced.

## Calcium/Vitamin D Supplementation

### Calcium, Vitamin D, and Fractures

Insufficient dietary calcium is one of the possible risk factors for osteoporosis and hence for frac-

tures. An inadequate intake of calcium is common in women; the NHANES data show that calcium intake in women is 40 to 50 percent below that of men, and 75 to 80 percent of women have daily intakes below 800 mg while 25 percent have intakes below 300 mg. According to the 1984 NIH consensus conference on osteoporosis, dietary calcium intake required to prevent negative calcium balance increases from around 1,000 mg/day in perimenopausal women to 1,500 mg/day after menopause. Intestinal absorption of calcium declines with advancing age. An age-related intestinal resistance to the action of 1,25(OH)<sub>2</sub>D has been implicated in this impaired absorption, as have age-related changes in parathyroid hormone and 1,25(OH)<sub>2</sub>D levels. Estrogen is known to enhance intestinal calcium absorption and renal calcium conservation. Thus, both estrogen and calcium supplementation can help reverse the negative calcium balance that accompanies aging. On the other hand, low-fat diets are often accompanied by a reduced intake of dairy products and calcium and may thus increase the negative calcium balance.

Even though low dietary calcium intake may be a risk factor for osteoporosis and for fractures, the data on the effectiveness of calcium supplements are conflicting. This variation may reflect differences in hormonal status and diet of the subjects. In a recent study of older postmenopausal women, calcium supplements were effective in preventing bone loss in those women with a dietary calcium intake of less than 400 mg but not in those with higher dietary calcium intakes. The addition of vitamin D appears to increase the effect of supplemental calcium on bone loss; it is uncertain whether this is because the absorption of calcium is enhanced or whether vitamin D exerts an independent effect. Estrogen therapy reduces bone loss in postmenopausal women, and it is not known whether calcium supplementation in women already on estrogen will induce a significant further reduction in bone loss.

Human observational studies and animal experiments suggest that calcium may decrease the risk of colorectal cancer, possibly because increased formation of the calcium salt of bile acids

decreases promotion of cancer. Data from controlled trials on the effect of calcium supplementation on colorectal cancer are not available; hence, this large trial may provide valuable information.

Despite the lack of data regarding efficacy, many women are currently taking supplements of calcium and vitamin D in the hope of reducing fractures. A clinical trial would provide a rational basis for advising women to take such supplementation. The trial will indicate whether supplementation is effective in reducing bone loss and fracture rates and in reducing colorectal cancer. A test for interactions may provide additional information on aspects such as the effect of supplementation alone or in combination with estrogens on fractures.

## ***Objectives of the Clinical Trial***

The overall objective of the trial will be to test the effectiveness of a number of treatments that may improve the health of postmenopausal women ages 50 to 79. The treatments to be tested are: hormone replacement therapy, low-fat dietary pattern, and supplementation with calcium and vitamin D. The aims for each treatment follow.

### **Hormone Replacement Therapy**

#### ***Primary aim:***

To test whether estrogen replacement and estrogen-progesterone replacement reduces the incidence of coronary heart disease and cardiovascular disease.

#### ***Subsidiary aims:***

1. To test whether estrogen replacement and estrogen-progesterone replacement reduces the incidence of fractures (hip, proximal humerus, distal radius, pelvis, vertebrae).
2. To assess whether estrogen replacement increases the risk of endometrial and breast cancer and whether these are reduced by estrogen-progesterone.

## Low-Fat Dietary Pattern

**Primary aim:**

To test whether a low-fat dietary pattern reduces the incidence of breast cancer and (separately) colorectal cancer.

**Subsidiary aim:**

To test whether a low-fat dietary pattern reduces the incidence of coronary heart disease.

## Calcium/Vitamin D Supplementation

**Primary aim:**

To test whether supplementation with calcium and vitamin D reduces the incidence of fractures.

**Subsidiary aim:**

To test whether supplementation with calcium and vitamin D reduces the incidence of colorectal cancer.

Even though the trial will not have sufficient power to test subgroup hypotheses unless unexpectedly large effects exist, various additional analyses will be conducted to explore whether the effects of treatments are likely to vary by patient characteristics or in the presence of another treatment. Subgroups that will be examined are:

1. The effect of hormone replacement therapy on the incidence of coronary and cardiovascular disease in women with, and in women without, coronary and cardiovascular disease at baseline.
2. The effect of hormone replacement therapy on the incidence of coronary and cardiovascular disease and breast cancer in obese and lean women.
3. The effect of supplementation with calcium and vitamin D in women with low, and women with high, intakes of dietary calcium.
4. The effect of hormone replacement therapy and of a low-fat dietary pattern in women at high and at low risk of breast cancer.

5. The effect of hormone replacement therapy plus low-fat dietary pattern on coronary disease and breast cancer compared with each therapy alone.
6. The effect of hormone replacement therapy plus calcium and vitamin D supplementation on fracture rates compared with each therapy alone.
7. The effects of treatments by age, in minorities, and in women of differing socioeconomic status.

The trial will offer the opportunity to examine certain other questions, such as: the effect of each treatment on overall quality of life; the effect of hormone replacement therapy and low-fat dietary pattern on lipids, lipoprotein, clotting factors, blood pressure, body mass index, waist-to-hip ratio, and blood glucose; the effect of hormone replacement therapy and calcium/vitamin D on bone density and biochemical markers of bone turnover; and the relationship to clinical outcomes of (1) baseline biochemical and physical variables, (2) changes in those variables induced by treatment, and (3) compliance.

## Recruitment, Randomization, and Follow-up

The Clinical Trial will be a partially blinded, controlled clinical trial of postmenopausal women ages 50 to 79. The treatments will be tested in a partial  $3 \times 2 \times 2$  factorial design. The first component will test the efficacy of estrogen replacement and estrogen-progesterone versus placebo on coronary heart disease (three arms); the second will test the efficacy of low-fat dietary pattern versus usual dietary pattern on breast and colorectal cancer (two arms); and the third will test the efficacy of calcium/vitamin D supplementation versus placebo on fractures (two arms). In regard to safety, clinical outcomes of interest include breast cancer and endometrial cancer (hormone replacement therapy), thromboembolism, and renal calculi (calcium/vitamin D supplementation).

The eligibility and exclusion criteria are as broad as possible to increase the generalizability of the

results to the population of postmenopausal women. Efforts will be made to ensure adequate representation of minority women and women of lower socioeconomic status. A feasibility study, funded by the National Cancer Institute and about 1 year ahead of this study, will assess methods and success rates for recruiting minority women and developing culturally sensitive diets and learning materials. It is envisaged that the women recruited in the feasibility study will be offered the opportunity to participate in the current proposed trial.

Women will be recruited on the basis of their eligibility and willingness to participate in either the hormone replacement therapy or the dietary modification components, or both. It is anticipated that the majority (64 percent) of women who are enrolled in the hormone replacement therapy component also will be enrolled in the dietary modification component and that 80 percent of women will be randomized into the calcium/vitamin D component. The total study population is likely to be in the range of 55,000-60,000.

## Inclusion Criteria

Women must be:

1. Between the ages of 50 and 79 years.
2. Postmenopausal, as established by absence of vaginal bleeding for at least 6 months if age 55 to 79; 1 year if age 50 to 54; or documented bilateral oophorectomy.
3. Be eligible and willing to participate in either the hormone replacement component or the dietary modification component or both.

## Exclusion Criteria

1. Recent (in the past 6 months) acute myocardial infarction or stroke.
2. History of breast cancer or endometrial cancer (for hormone replacement therapy component).

3. Endometrial biopsy showing hyperplasia (for hormone replacement component) or baseline mammogram suggestive of breast cancer.
4. Invasive cancer in the past 5 years or other conditions that could shorten survival to less than 5 years or disabilities that would preclude participation in a long-term trial.
5. Active thromboembolic disease (for hormone replacement component).
6. Inability or unwillingness to discontinue estrogens (for the hormone replacement component) or calcium or vitamin D supplements (for the calcium/vitamin D component).
7. Previous osteoporosis-related fracture(s) being treated with hormones (for hormone replacement component).
8. Previous administration of diethylstilbestrol (DES) (for hormone replacement component).
9. History of renal stones (for the calcium/vitamin D component).
10. Less than 38 percent fat in the diet (for the dietary modification component).
11. Unable to complete successfully the baseline dietary report(s) required during the eligibility screening process (for the dietary modification component).

## Sample Size

Sample size calculations indicate that for the hormone replacement therapy-coronary heart disease component, 25,000 women will need to be treated for an average of 9 years. The dietary modification-cancer component would need 48,000 women treated for an average of 9 years. For the calcium/vitamin D-fracture component, a sample size of 45,000 women is envisaged. Post-trial surveillance for a future 5 years is envisaged so that total follow-up will be an average of 14 years. Mortality will be followed by monitoring the

National Death Index, and breast cancer incidence will be monitored by repeat contacts with participants for a minimum period of 5 years posttrial.

## Dietary Intervention

The two main hypotheses of the dietary intervention component are that breast cancer incidence and colorectal cancer incidence will be reduced. A secondary hypothesis is that coronary heart disease will be reduced. Power calculations were done for each of these three main hypothesis. The assumptions for these power calculations include:

1. A randomization ratio of 40:60 for dietary intervention:no dietary intervention.
2. One-sided test of significance at  $\alpha = 0.025$ .
3. The log-rank test will be used to compare the rates of disease between groups.
4. Average duration of followup, 9 years.
5. Age distribution in 3 10-year age intervals of 50-59, 60-69, and 70-79 = 2:2:1.
6. Loss to followup/competing risk: 3 percent per annum for cancers of breast and colon/rectum; 2 percent per annum for coronary heart disease.
7. Anticipated intervention effect for breast cancer, 17 percent; for colorectal cancer, 25 percent; for coronary heart disease, 12 percent.
8. Incidence rates of breast and colorectal cancer were obtained from the Surveillance, Epidemiology, and End Result (SEER) program, and for coronary heart disease from the national coronary heart disease mortality rates, corrected for secular trend and multiplied by a factor of 2.5 to give incidence rates of fatal plus nonfatal coronary heart disease. A healthy volunteer effect of 67 percent was applied to the coronary heart disease rates, but not to the cancer rates (as breast and colorectal cancer are not strongly related to socioeconomic status or previous ill-health).

Based on these assumptions, a sample size of 48,000 will provide 90-94 percent power for each of the end points breast cancer, colorectal cancer, and coronary heart disease.

## Hormone Replacement Therapy

Women will be randomized to one of three groups: Estrogen Replacement Therapy (ERT), Progestin/Estrogen Replacement Therapy (PERT), or Placebo (P). The main hypothesis is that ERT (or PERT) reduces coronary heart disease incidence. Secondary hypotheses are that ERT (or PERT) reduces cardiovascular disease incidence and the incidence of fractures. With regard to undesirable effects, there is interest in testing for a possible increase due to ERT in the incidence of breast cancer. Assumptions of the power calculations for each of these tests are:

1. Randomization ratio 30:30:40 for ERT:PERT:Placebo.
2. Significance level 2-sided test at  $\alpha = 0.05$ .
3. The log-rank test will be used to compare the rates of incident coronary heart disease in the ERT vs. Placebo groups and the PERT vs. Placebo groups.
4. Average duration of followup, 9 years (14 years for breast cancer).
5. Age distribution equal in 3 10-year age intervals 2:2:1.
6. Loss to follow-up/competing risk: 2 percent per annum.
7. Drop-out: in year 1, 5 percent of women in the ERT (or PERT) group will switch to Placebo and 2.5 percent per year thereafter.
8. Drop-in: up to year 6, 1.2 percent women on Placebo will switch to ERT (or PERT). For years 6-10, this annual rate will fall to 1 percent.
9. Lag: 1 year.
10. Anticipated intervention effect: for coronary heart disease, 30 percent; for fractures, 30

- percent. Power for a possible adverse effect on breast cancer incidence of 30 percent at 14 years has also been calculated.
11. Incidence rates: as for dietary intervention for coronary heart disease, cardiovascular disease, breast cancer. For fractures, the data from the Mayo Clinic were used, adjusted by 20 percent to account for fractures at multiple sites and by a healthy volunteer effect of 80 percent.

Based on these assumptions, a sample size of 25,000 will give 89 percent power for coronary heart disease, 99.9 percent power for cardiovascular disease, 99 percent power for fractures, and 85 percent power for breast cancer.

## **Calcium/Vitamin D Supplementation**

It is estimated that 80 percent of women in the trial (i.e., 45,000) will be willing and eligible to be randomized into the calcium/vitamin D supplementation. Statistical power for detecting an effect on fractures will be considerably in excess of the power for ERT on fractures, since the sample size is so much larger. In particular for a sample size of 45,000, power for detection of an effect on hip fractures after 9 years of followup is 86 percent for a 25 percent reduction in incidence, 96 percent for a 30 percent reduction, and 99 percent for a 35 percent reduction. For the effect of calcium/vitamin D on colorectal cancer, power will be similar to that shown for dietary modification.

## **Choice of Treatments and Outcomes of Interest**

### **Hormone Replacement Therapy Component**

The clinical outcomes of interest in regard to efficacy are the incidence of coronary heart disease events (fatal plus nonfatal), cardiovascular events (fatal plus nonfatal), fractures (of proximal femur, proximal humerus, distal radius, pelvis, and vertebrae), and total mortality. For safety, additional outcomes of interest will be monitored, including

breast cancer, endometrial cancer, thromboembolic disease, and cholecystitis.

The intermediate outcomes of interest are blood lipids and lipoproteins, including total cholesterol, LDL cholesterol, HDL cholesterol, HDL cholesterol subfractions, triglycerides, and Lp(a); fibrinogen; blood glucose; blood pressure; body weight; height; ratio of waist-to-hip circumference; bone density; and possibly, markers of bone turnover. Changes in the psychosocial domains (and in particular, quality of life) will be assessed, for example, depression, cognition, functional status, social well-being, life satisfaction, social support, and general well-being.

## **Dietary Modification Component**

The dietary intervention's goal will be to reduce total fat (20 percent of calories) and saturated fat intake (less than 7 percent of calories) and to increase complex carbohydrate and fiber-containing foods to five or more daily servings for fruits and vegetables and to six or more daily servings for grain products. This dietary goal has been selected on the basis of epidemiologic data and on the basis of feasibility. In pilot studies, U.S. women have been able to achieve a fat intake close to 20 percent of calories.

The nutrition program for the intervention group will be a nutrition education and counseling approach aimed at providing the women with skills necessary to make a permanent lifestyle change to a low-fat eating plan. The program integrates knowledge and skills from both nutritional and behavioral sciences and uses a small group format and a self-reliant, self-directed approach. The general strategy incorporates teaching nutrition skills, self-monitoring techniques, and group support systems. Women in the intervention group will meet in small groups. Each group will be assigned a nutritionist who will serve as an educator, facilitator, and counselor throughout the study. The intervention program will begin with six weekly sessions, then six biweekly sessions, and then monthly sessions for the next 9 months. Thereafter, groups will meet four times per year.

Women in the control group will not be offered a nutrition intervention program because the general strategy to be adopted for this group will be minimum interference with customary diets while collecting nutritional data considered necessary for appropriate comparison with the nutrition intervention group. Participants in the control group will be provided a standard packet of materials, including information on basic nutrition principles for maintaining nutritionally adequate diets, and given a copy of the *USDA/DHHS Dietary Guidelines for Americans (3rd Edition)*. Both the dietary modification and control groups will be advised to follow a program of moderate exercise (e.g., walking for half an hour per day), and smokers will be advised to stop.

The clinical outcomes of interest are incidence of breast cancer, colorectal cancer, coronary heart disease (fatal plus nonfatal), and total mortality.

The intermediate outcomes of interest are blood lipids and lipoprotein (total cholesterol, LDL cholesterol, HDL cholesterol, HDL cholesterol subfractions, triglycerides, and Lp(A)), fibrinogen, blood glucose, blood pressure, body weight, height, and ratio of waist-to-hip circumference.

## **Calcium and Vitamin D Component**

Chewable calcium carbonate at a dose of 500 mg daily or 300 mg two times daily with meals has tentatively been selected. For vitamin D, it is proposed to use 400 IU daily of vitamin D<sub>3</sub>. This is a dose large enough to ensure adequacy without risking toxicity. Calcium and vitamin D<sub>3</sub> administration at these doses do not need medical supervision provided that subjects with nephrolithiasis are excluded; these agents are available over-the-counter and are widely self-administered.

The clinical outcomes of interest in regard to efficacy are the incidence of fractures at all sites, and hip fractures in particular, and the incidence of colorectal cancer. In regard to safety, the incidence of renal calculi is of interest.

The intermediate outcomes of interest are height, bone density, and possibly, markers of bone turnover.

## **Recruitment**

Age-eligible (50 to 79 years) women will be invited to attend one of the clinical centers for a screening visit. Women who attend visit 1 may be willing to enter the clinical trial or may be willing to participate in the observational study only. A total of 55,000 to 60,000 women are needed for the trial, and it is anticipated that 100,000 will be enrolled in the observational component (grand total 155,000-160,000). Approximately 45 centers, each recruiting about 1,300 participants for the trial and another 2,200 for the observation component, will be required to recruit the women over a 3-year period. Women who are eligible and willing will be entered into the trial, and women who are not eligible and/or willing will be entered into the observational component (described subsequently).

## **Screening Visit**

As far as possible, women will be prescreened for eligibility and willingness to participate in either the trial or observational components, for example, by the use of key questions on postcards or over the telephone. Women will be asked to fast for 12 hours prior to the clinic visit. Women who attend the clinic without prior contact similarly will be initially screened to ascertain likely eligibility and interest. If women were not fasting at the first visit, bloods will be drawn at a subsequent visit. The women will be informed about the study and asked to complete a short demographic questionnaire and a limited informed consent before having tests started. They will be asked to indicate which of the dietary modification or hormone replacement (or both) components they are willing to participate in.

Women consenting to enter the clinical trial will have baseline psychosocial, assessment of risk factors for the diseases under study, dietary pattern, laboratory determinations for monitoring, an electrocardiogram, and mammogram. Repeat visits will be made semiannually by all participants, mammograms will be repeated annually, and electrocardiograms every 3 years. Women random-

ized to estrogen replacement will have baseline and annual endometrial aspirations.

## Safety and Toxicity Monitoring

Safety and toxicity monitoring will be conducted on all participants on return clinic visits. An independent Data and Safety Monitoring Board, appointed by the Director of NIH, will periodically review the trial with respect to recruitment, compliance to protocol, compliance to intervention, clinical outcomes, and participant safety. This group will make recommendations to NIH concerning the continuation or early termination to part or all of the trial. The number of interventions and the number of comparisons for efficacy and safety will make monitoring this trial a complex undertaking. In a trial with multiple end points, it is difficult to devise stopping rules. A rule that is appropriate for one component may infringe on the success of another component. It is estimated that the interventions will require 9 years to accumulate sufficient outcomes to provide confident estimates of effect. Follow-up for an additional 5 years is envisaged so that late effects of hormone replacement therapy on breast and endometrial cancer can be monitored. Compliance to intervention will be assessed at 1 and 2 years to allow recommendations regarding the further continuation of each of the components of the trial. Interim analyses will be performed by the coordinating center for use by the Data and Safety Monitoring Board. The Data and Safety Monitoring Board will carefully monitor all potential side effects and adverse effects, with special attention to some subgroups at greater risk of adverse outcomes (e.g., women with a family history of breast cancer) and make appropriate recommendations with respect to patient safety.

## *Observational Component*

There is general recognition that too few mature women have been studied longitudinally and that major questions remain about prediction of chronic diseases in postmenopausal women. This initiative and particularly the recruitment for the

clinical trial component present an opportunity to accumulate a large cohort of women, to follow them, and to determine the predictors and biological markers of disease. Integration of these observational studies into the trial component is an efficient and effective way to achieve the following objectives:

1. Screen individuals for participation in the randomized clinical trials.
2. Develop risk-factor analyses for cardiovascular disease, cancer, and osteoporosis.
3. Conduct surveillance of deaths and hospital admissions for cardiovascular disease, coronary heart disease, stroke, cancer, and fractures. Assess psychosocial, including quality of life, changes over time.
4. Use the case-control approach to study the link between subclinical markers and clinical disease.

## Study Population

All age-eligible women (50 to 79 years) will be enrolled in the observational study. It is estimated that about one-third of all women screened will enter the clinical trial (55,000-60,000), and the other two-thirds will enter the observational study (100,000). The observational study will include those women who are ineligible, unable, or unwilling to participate in the intervention trial. At minimum, much of the same baseline data and follow-up will be available as for the clinical trial participants. Informed consent will be obtained to collect information and a blood specimen. Blood obtained from all volunteers will be separated into fractions and stored frozen for future analysis.

Women of all races, ethnic groups, and socioeconomic levels will be included. Stratification of recruitment on a 10-year age group is proposed to meet trial needs and to ensure that adequate numbers of events will occur during the first few years of follow-up.

Women for more detailed baseline and follow-up examinations may be recruited at field centers

that propose to undertake this component of the study and that have the necessary expertise and resources.

## Study Design

The Observational Study is a longitudinal prospective observational study of a large cohort of 50- to 79-year-old women. Information collected at entry to the study will be used for cross-sectional or prevalence data analysis.

Baseline assessments will include personal medical history, psychosocial assessment, and physical measurements. Blood will be obtained and separated into aliquots of red cells, white cells, and sera and stored at -70°C for future analysis.

A subsample of women in the observational cohort will be reexamined at 3 years after initial examination. This will provide an assessment of change in physiological measurements and provide an opportunity to link these changes to disease development. A more detailed psychosocial assessment will be done at this visit.

All women will be followed by mailed questionnaires and through the National Death Index to ascertain hospitalizations and deaths attributed to cardiovascular diseases, cancer, fractures, and other causes. In areas covered by state cancer registers or SEER data, incident cases of cancer can be found.

As new events are detected, nested case-comparison studies will be undertaken to detect associations between biochemical, psychosocial, genetic, or pathophysiological characteristics and events of interest.

## Funding and Management of the Study

This research will be supported through the contract mechanism. A solicitation for proposals will be announced, and investigators will be invited to respond according to specifications in this

request. These proposals will be reviewed competitively. Selection criteria will be weighted to ensure adequate representation of minorities, rural areas, and geographic regions. The coordinating center and 15 clinical centers will initially be selected, and these will form a vanguard which will develop the study protocol and test and streamline recruitment, management, and intervention strategies. The remainder of the clinical centers will subsequently be solicited and selected and will begin recruitment approximately 1 year after the vanguard centers. It is estimated that 1 coordinating center and 45 clinical centers will eventually be funded and constitute the full phase of the studies. Solicitation for the coordinating center and 15 vanguard clinical centers was completed on June 30, 1992. When these centers have been selected, the final protocol will be developed collaboratively, and common recruitment and training programs will be set up. Recruitment, randomization, and measurement will begin.

The development of this plan and the subsequent management of the study will be coordinated by the Office of Disease Prevention and Office of Research on Women's Health, both of which are under the Office of the Director, NIH. An oversight committee made up of persons having a broad range of relevant expertise and background will review and monitor progress and conduct of all aspects of the studies. This committee will report to the Director of NIH. Separate Data and Safety Monitoring Boards will be set up for the Clinical Trial/Observational component and for the Community Trial.

These committees will meet about every 6 months to monitor the progress of recruitment; status of data management, toxicity, and adverse effects; and evidence of efficacy. They will recommend to the Director of NIH whether to continue or stop the studies.

## APPENDIX 2

### ***Task Force on Opportunities for Research on Women's Health***

#### **Chair**

**Ruth L. Kirschstein, M.D.**

Director

National Institute of General Medical Sciences  
Former Acting Director  
Office of Research on Women's Health  
National Institutes of Health  
Westwood Building, Room 926  
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#### **Members**

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**Jane Delgado, Ph.D.**

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The National Coalition of Spanish Health and Human  
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**William R. Hazzard, M.D.**

Professor and Chairman

Department of Internal Medicine  
Director

J. Paul Stricht Center on Aging  
Bowman Gray School of Medicine  
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**Shiriki K. Kumanyika, R.D., Ph.D., M.P.H.**

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**Elaine A. Leventhal, M.D., Ph.D.**

Robert Wood Johnson School of Medicine  
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New Brunswick, New Jersey 08903

**Robert Lindsay, Ph.D.**

Professor of Clinical Medicine  
College of Physicians and Surgeons  
Columbia University  
Director  
Regional Bone Center  
Chief  
Internal Medicine  
Helen Hayes Hospital  
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West Haverstraw, New York 10993

**Judy Norsigian**

Co-Director  
Boston Women's Health Book Collective  
Board Member  
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**Mary Lake Polan, M.D.**

Professor and Chairman  
Department of Obstetrics and Gynecology  
Stanford University School of Medicine  
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*Frank G. Standaert, M.D.*

Director of Research  
Research Department  
Toledo Hospital  
Professor of Pharmacology and Anesthesiology  
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*Nancy F. Woods, Ph.D., R.N., F.A.A.N.*

Professor  
University of Washington  
Director  
Center for Women's Health Research  
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**Liaison Member, Advisory  
Committee to the Director, NIH**

*Patricia King, J.D.*

Professor of Law  
Georgetown University Law Center  
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Washington, D.C. 20001

# APPENDIX 3

## *Organizations Testifying at the Public Hearing Before the Task Force on Opportunities for Research on Women's Health*

**June 12-13, 1992**

### *Oral Testimony*

#### **American College of Clinical Pharmacy**

*Robert M. Elenbaas, Pharm.D., F.C.C.P.*  
Executive Director  
Suite 380  
3101 Broadway  
Kansas City, Missouri 64111  
(Rosalie Sagraves, Pharm.D., testifying)

#### **(The) American College of Obstetricians and Gynecologists**

*Kathy Bryant*  
Associate Director, Government Relations  
409 Twelfth Street, S.W.  
Washington, D.C. 20024-2188  
(Luella Klein, M.D., F.A.C.O.G., testifying)

#### **American College of Rheumatology**

*Amanda L. Spitler*  
Government Affairs Representative  
Suite 150  
60 Executive Park South  
Atlanta, Georgia 30329  
(Barbara Needleman, M.D., testifying)

#### **American College of Surgeons**

*Paul A. Ebert, M.D., F.A.C.S.*  
Director  
55 East Erie Street  
Chicago, Illinois 60611  
(Margaret F. Longo, M.D., F.A.C.S., testifying)

#### **(The) American Fertility Society**

*Robert D. Visscher, M.D.*  
Medical Director  
Suite 200  
2140 Eleventh Avenue South  
Birmingham, Alabama 35205-2800  
(Marian Damewood, M.D., testifying)

#### **American Heart Association**

*Scott Ballin, J.D.*  
Vice President and Legislative Counsel  
Suite 360  
1250 Connecticut Avenue, N.W.  
Washington, D.C. 20036  
(John C. LaRosa, M.D., testifying)

#### **American Medical Women's Association, Inc.**

*Lois Schoenbrun*  
Deputy Executive Director  
Suite 400  
801 North Fairfax Street  
Alexandria, Virginia 22314  
(Roselyn Payne Epps, M.D., M.P.H., testifying)

#### **American Nurses' Association**

*Barbara Redman, Ph.D., R.N., F.A.A.N.*  
Department of Congressional and Agency Relations  
Suite 200  
1101 Fourteenth Street, N.W.  
Washington, D.C. 20005  
(Dr. Redman testifying)

**(The) American Psychological Association  
and the Federation of Behavioral,  
Psychological and Cognitive Sciences**

*Barbara J. Calkins, APA*

*Claudia Feller, FBPCS*

1200 Seventeenth Street, N.W.  
Washington, D.C. 20036

(Gwen Keita, Ph.D., testifying)

**American Public Health Association**

*Charles P. Schade, M.D., M.P.H.*

Associate Executive Director

Professional Affairs Division  
1015 Fifteenth Street, N.W.

Washington, D.C. 20005

(Carol S. Weisman, Ph.D., testifying)

**American Society for Microbiology**

*Janet Shoemaker*

Assistant Director, Public Affairs

1325 Massachusetts Avenue, N.W.

Washington, D.C. 20005

(Gail Cassell, Ph.D., testifying)

**American Society of Clinical Oncology**

*Stacey Beckhardt*

Director, Government Relations

Suite 1100

750 Seventeenth Street, N.W.

Washington, D.C. 20006

(Jane Henney, M.D., testifying)

**Association for Women in Science**

*Stephanie J. Bird, Ph.D.*

President

Suite 820

1522 K Street, N.W.

Washington, D.C. 20005

(Dr. Bird testifying)

**Breast Cancer Action Group**

*Virginia Soffa, M.Ed.*

President

P.O. Box 5605

Burlington, Vermont 05402

(Ms. Soffa testifying)

**(The) Breast Cancer Coalition**

*Susan Love, M.D.*

Director, Faulkner Breast Center

1153 Centre Street

Jamaica Plain, Massachusetts 02130

(Dr. Love testifying)

**Cancer Patients Action Alliance, Inc.**

*Beverly Zakarian*

President

26 College Place

Brooklyn, New York 11210

(Ms. Zakarian testifying)

**Center for Women's Policy Studies**

*Leslie R. Wolfe, Ph.D.*

Executive Director

Suite 508

2000 P Street, N.W.

Washington, D.C. 20036

(Dr. Wolfe testifying)

**COGS Women's Support Group**

*Mary G. Bonk, R.N.*

225 Glencourtney Drive, N.E.

Atlanta, Georgia 30328

(Ms. Bonk testifying)

**Consortium of Social Science Associations**

*Judith D. Auerbach, Ph.D.*

Government Liaison

Suite 836

1522 K Street, N.W.

Washington, D.C. 20005

(Dr. Auerbach testifying)

**DES Action USA**

*Nora Cody*

Executive Director

Suite 510

1615 Broadway

Oakland, California 94612

(Margaret Lee Braun testifying)

**Endometriosis Alliance of Metropolitan Washington, Inc.**

*Lea Christy Sloan*

Member, Board of Directors

P.O. Box 11695

Washington, D.C. 20008

(Binaifer Davar testifying)

**Endometriosis Association**

*Mary Lou Ballweg*

President and Executive Director

International Headquarters

8585 North 76th Place

Milwaukee, Wisconsin 53223

(Ms. Ballweg testifying)

**Endometriosis Institute of Oregon**

*Debra Redwine, CPA*

Deputy Director and Comptroller

2190 N.E. Professional Court

Bend, Oregon 97701

(Ms. Redwine testifying)

**Family Health International**

*William P. Schellstede*

Executive Vice President

P.O. Box 13950

Research Triangle Park, North Carolina 27709

(Arlene McKay, Ph.D., testifying)

**(The) Federation of Behavioral,  
Psychological and Cognitive Sciences and  
The American Psychological Association**

*Barbara J. Calkins (APA)*

*Claudia Feller (FBPCS)*  
1200 Seventeenth Street, N.W.  
Washington, D.C. 20036  
(Gwen Keita, Ph.D., testifying)

**(The) Feminist Majority Foundation**

*Eleanor Smeal*

President  
Suite 704  
1600 Wilson Boulevard  
Arlington, Virginia 22209  
(Ms. Smeal testifying)

**GMHC-Gay Men's Health Crisis, Inc.**

*Catherine A. Lynch*

Policy Associate  
129 West 20th Street  
New York, New York 10011-0022  
(Ms. Lynch testifying)

**HIV Center for Clinical and Behavioral  
Studies**

*Anke A. Ehrhardt, Ph.D.*

Professor and Director  
New York State Psychiatric Institute  
722 West 168th Street  
New York, New York 10032  
(Dr. Ehrhardt testifying)

**Institute of Medicine Food and Nutrition  
Board**

*Catherine E. Woteki, Ph.D., R.D.*

Director  
National Academy of Sciences  
2101 Constitution Avenue, N.W.  
Washington, D.C. 20418  
(Dr. Woteki testifying)

**Institute for Research on Women's Health**

*Margaret Jensvold, M.D.*

Director  
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1616 Eighteenth Street, NW.  
Washington, D.C. 20009  
(Dr. Jensvold testifying)

**Interstitial Cystitis Association**

*Debra Slade*

Executive Director  
P.O. Box 1553  
Madison Square Station  
New York, New York 10159  
(Vicki Ratner, M.D., testifying)

**Interstitial Cystitis Association of  
America, Inc.**

*Lana Fayman*

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San Diego, California 92175  
(Elizabeth White testifying)

**Keys-Page Media Group**

*Marilyn Keys and Laura Page*

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(Ms. Keys testifying)

**(The) Lupus Foundation of America, Inc.**

*John M. Huber*

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Four Research Place  
Rockville, Maryland 20850-3226  
(Barbara D. Butler testifying)

**Lynne Warrick Enterprises, Inc.**

*Lynne Warrick*

President  
Suite 105  
8350 Greensboro Drive  
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(Ms. Warrick testifying)

**Magee-Womens Hospital**

*Irma E. Goertzen*

President and Chief Executive Officer  
Forbes Avenue and Halket Street  
Pittsburgh, Pennsylvania 15213  
(Ms. Goertzen testifying)

**NAACOG—The Organization for Obstetric,  
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*Jette Engstrom*

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(Carolyn M. Sampselle, Ph.D., R.N.C., testifying)

**(The) National Association of Women's  
Health Professionals**

*Patty Looker*

Executive Director  
Suite 700  
500 Davis Street  
Evanston, Illinois 60201  
(Ms. Looker testifying)

**(The) National College of Chiropractic**

*Dr. Patricia Brennan*

Dean of Research  
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(Marion McGregor, D.C., M.Sc., testifying)

**National Headache Foundation**

*Suzanne E. Simons*

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5252 North Western Avenue  
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(Ms. Simons testifying)

**National Organization for Women, Inc.**

*Molly Yard*

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Washington, D.C. 20036-5705  
(Patricia Ireland testifying)

**National Osteoporosis Foundation**

*Sandra C. Raymond*

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(Ms. Raymond testifying)

**National Sjogren's Syndrome Association**

*Barbara Henry*

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3201 West Evans Drive  
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(Ms. Henry testifying)

**National Women's Health Network**

*Cynthia Pearson*

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(Beverly F. Baker testifying)

**National Women's Health Resource Center**

*Norene Pease*

Executive Director  
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Washington, D.C. 20037  
(Deborah I. Dingell testifying)

**North County Coastal San Diego CFID Support Group**

*Meghan Shannon*

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P.O. Box 1135  
Cardiff, California 92007  
(Ms. Shannon testifying)

**Northern California Breast Cancer Organization**

*Sheila Swanson R.N.*

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19305 Crisp Avenue  
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(Ms. Swanson testifying)

**Nursing Network on Violence Against Women**

*Jacquelyn C. Campbell, Ph.D., R.N., F.A.A.N.*

Associate Professor  
Wayne State University College of Nursing  
5557 Cass Avenue  
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(Dr. Campbell testifying)

**(The) Older Women's League**

*Joan Kuriansky*

Executive Director  
Suite 300  
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**Paralyzed Veterans of American Spinal Cord Research Foundation**

*Cheryl M. Chanaud, Ph.D.*

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*Robin Monsky*

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(Ms. Monsky testifying)

**Sjogren's Syndrome Foundation, Inc.**

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(Kathy Hammitt testifying)

**Society for the Advancement of Women's Health Research**

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(Dr. Bustillo testifying)

**Systemic Lupus Erythematosus**

*Sharon Grant-Henry, Ph.D.*

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(Dr. Grant-Henry testifying)

**(The) TMJ Association, Ltd.**

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(Ms. Cowley testifying)

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**University of Cincinnati Health Science****Center***Mary Jane Jesse, M.D.*

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 (Dr. Jesse testifying)

**(The) University of Texas M.D. Anderson  
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 (Ms. Overlan testifying)

**Women's Health Focus***Joanne Hughes, R.N., M.Ed.*

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 (Ms. Hughes testifying)

**Women's International Public Health  
 Network***Naomi Baumslag, M.D., M.P.H.*

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**Duke University Medical Center**

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**(The) Forum on Breast Cancer Screening in  
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*Irene Pollin*  
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### **National Coalition for Cancer Survivorship**

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### **Simon Fraser University**

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### **Virginia Breast Cancer Foundation**

*Mary Jo Ellis Kahn*  
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### **Women's Health Focus**

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# APPENDIX 4

## *Workshop on Opportunities for Research on Women's Health*

*September 4-6, 1991  
Marriott's Hunt Valley Inn  
Hunt Valley, Maryland*

### *Agenda*

#### **Wednesday, September 4**

8:00 a.m.	Welcome	<i>Ruth L. Kirschstein, M.D. Acting Director, Office of Research on Women's Health</i>
8:15 a.m.	The Congressional Caucus for Women's Issues	<i>Representative Patricia Schroeder (D-Colorado)</i>
8:30 a.m.	Overview of the Status of Women's Health	<i>Maureen M. Henderson, M.D.</i>
9:15 a.m.	Workshop Objectives, Expected Workshop Outcome, and Working Group Report	Workshop Cochairs: <i>William R. Hazzard, M.D. Mary Lake Polan, M.D.</i>
9:30 a.m.	Discussion	<i>Ruth L. Kirschstein, M.D.</i>
9:45 a.m.	Charge to the Life Span Working Groups	<i>Mary Lake Polan, M.D.</i>
10:00 a.m.	Break	

## Wednesday, September 4 (continued)

10:30 a.m.	Concurrent Working Sessions: Life Span	<ul style="list-style-type: none"><li>■ Birth to Young Adulthood</li><li>■ Young Adulthood to Perimenopausal Years</li><li>■ Perimenopausal Years to Mature Years</li><li>■ Mature Years</li></ul>	Cochairs: <i>Alain Joffe, M.D., M.P.H. Roselyn Payne Epps, M.D.</i>
			Cochairs: <i>Gloria E. Sarto, M.D., Ph.D. Judith N. Wasserheit, M.D., M.P.H.</i>
			Cochairs: <i>Trudy L. Bush, Ph.D., M.H.S. Katie Miller-Bass, M.D., M.H.S.</i>
			Cochairs: <i>Robert Butler, M.D. Elaine A. Leventhal, M.D., Ph.D.</i>
12:00 p.m.	Luncheon		
	Keynote Address		
	<i>Research on Women's Health: Expanding the Horizons of Biomedical Science</i>		<i>Bernadine Healy, M.D. Director, National Institutes of Health</i>
1:30 p.m.	Continuation of Concurrent Working Sessions: Life Span		
4:30 p.m.	Adjourn	(Meeting of Life Span Cochairs to prepare working group recommendations)	

## Thursday, September 5

8:00 a.m.	Special Issues in Biomedical Research on Women	<ul style="list-style-type: none"><li>■ Issues of Recruiting and Retaining Study Participants Among Special Populations</li><li>■ Ethical and Legal Issues</li><li>■ Women's Health Advocacy</li></ul>	Cochairs: <i>Hortensia Amaro, Ph.D. Frank G. Standaert, M.D. Diane B. Stoy, R.N., M.A.</i>
			<i>Carol Levine Jean A. King, Ph.D.</i>

## Thursday, September 5 (continued)

9:30 a.m.	Brief Presentations and Discussion of Life Span Working Group Recommendations	
10:30 a.m.	Charge to Crosscutting Science Working Groups	<i>William R. Hazzard, M.D.</i>
10:45 a.m.	Concurrent Working Sessions: Crosscutting Science	
	■ Reproductive Biology	Cochairs: <i>Ernst Knobil, Ph.D.</i> <i>Michelle P. Warren, M.D.</i>
	■ Early Developmental Biology	Cochairs: <i>Brigid L.M. Hogan, Ph.D.</i> <i>Jerome F. Strauss, III, M.D., Ph.D.</i>
	■ Aging Processes	Cochairs: <i>Shiriki K. Kumanyika, Ph.D., R.D., M.P.H.</i> <i>Ramon Velez, M.D., M.Sc.</i>
	■ Cardiovascular Function and Disease	Cochairs: <i>Thomas B. Clarkson, D.V.M.</i> <i>Pamela S. Douglas, M.D.</i>
	■ Malignancy	Cochairs: <i>Michele K. Evans, M.D.</i> <i>Robert C. Young, M.D.</i>
	■ Immune Function and Infectious Diseases	Cochairs: <i>Thomas C. Quinn, M.D., M.Sc.</i> <i>Patience H. White, M.D.</i>
12:00 p.m.	Luncheon  <i>Women in Science Careers</i>	  <i>Shirley M. Tilghman, Ph.D.</i> <i>Professor, Department of Molecular Biology</i> <i>Princeton University</i>
1:00 p.m.	Continuation of Concurrent Working Sessions: Crosscutting Science	
4:00 p.m.	Adjourn  (Meeting of Crosscutting Science Cochairs to prepare working group recommendations)	

## **Friday, September 6**

8:00 a.m.	Presentations and Discussion of Crosscutting Science Working Group Recommendations	
9:00 a.m.	Discussion of Common Themes and Priority Recommendations for Opportunities for Research on Women's Health	
10:30 a.m.	Break	
11:00 a.m.	Recommendations, Priorities, and Common Themes for Opportunities for Research on Women's Health	<i>William R. Hazzard, M.D. Mary Lake Polan, M.D.</i>
12:30 p.m.	Adjourn  (Administrative meeting of all Cochairs and ORWH Staff to discuss process for submission of draft documents)	

# APPENDIX 5

## *Workshop on Opportunities for Research on Women's Health*

**Marriott's Hunt Valley Inn  
Hunt Valley, Maryland  
September 4-6, 1991**

### *List of Attendees*

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# APPENDIX 6

***Recommendations for Research  
on Women and HIV Infection  
National Conference on Women  
and HIV Infection***

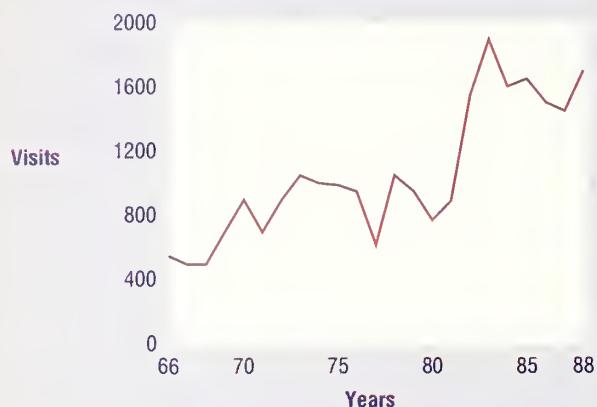
The first National Conference on Women and HIV Infection, held in December 1990, was sponsored by the agencies of the Public Health Service (PHS). Following the conference, recommendations for further research were developed by a core group of community health care providers, advocates, women with HIV infection, researchers, and PHS representatives who participated in conference planning and followup activities. The draft document was circulated to additional community members, and their comments have been incorporated into the following recommendations that will be made available to PHS agencies for their use in planning programs and research relevant to women and HIV infection.

Central to these recommendations is the recognition that the multiple problems faced by women with HIV infection present a challenge that can be met only through increased attention to psychosocial and behavioral as well as biomedical research needs. This effort will require increased collaboration between government agencies and formally established partnerships among government agencies, traditional academic research facilities, and community groups.

## ***General Recommendations***

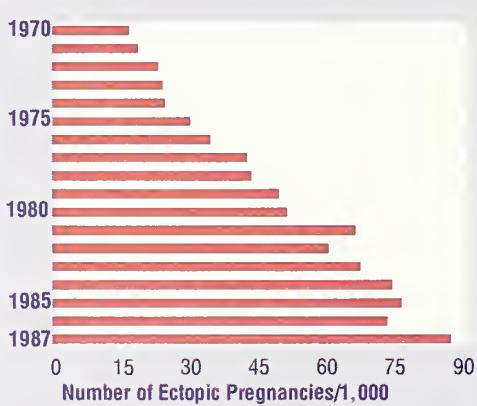
1. Enhance the existing effort to inform Scientific Review Administrators (SRA) and study section members about the need to include women and minorities in clinical trials by increasing their competency to identify the special needs of women and minorities who are at risk for and infected with HIV. Conduct training of institute staff on culturally appropriate methods and philosophies that support the inclusion of women and people of diverse ethnic and cultural groups in HIV/AIDS research.
2. Facilitate the ongoing review of existing policies and consideration of new policies to increase the inclusion of women (pregnant and non-pregnant) in clinical drug trials and to promote gender-specific research in all phases of drug development.
3. Support research that incorporates such characteristics as participation of women in clinical drug trials and HIV/AIDS research; partnerships with community organizations, community advisory boards, community updates of research progress, and community feedback mechanisms; integrated research, treatment,

**Figure 1.**  
**Trends in Physician Consultations for Infertility (U.S. 1966-88)\***



Source: IMS America, Ltd., National Disease and Therapeutic Index.

**Figure 2.**  
**Estimated Number of Ectopic Pregnancies United States, 1970-1987**



Source: National Hospital Discharge Survey, National Center for Health Statistics.

agement, transportation, and child care); and community-based and street outreach to enroll women in clinical and prevention studies.

Representatives of the population being studied should be included on the research team.

4. Provide supplemental funding on regular research project grants to increase the number of women, minorities, and primary care providers participating in research on women and HIV infection.
5. Provide information to the community on research opportunities, criteria for review of grant applications, and research findings, in a timely manner.
6. Priority should be given to applicants who demonstrate substantive involvement and collaboration with community physicians, allied health service providers, and community service providers in review criteria for clinical trials, epidemiologic studies, and other research activities targeted to women and minorities.
7. Develop a program involving PHS and particularly NIH staff to provide advice and technical assistance to community-based organizations for development and preparation of grant applications for HIV/AIDS research. Provide funds and assistance for data collection.
8. Establish a mechanism for development of collaborative activities, partnerships, and initiatives on HIV in women involving patient advocates, PHS staff, researchers, physicians, and "front line" health and social service providers.
9. Emphasize the term HIV infection (rather than AIDS) in education/prevention activities and focus prevention efforts on HIV as a sexually transmitted infection. Incorporate concepts of class, gender, literacy level, and multicultural values and belief systems into research methodology and programs.
10. Establish a national clearinghouse on women's health to educate the public, collect and disseminate resource information, and provide an updated directory of ongoing research activities and community programs on all aspects of women's health, including HIV/AIDS.

## **Biomedical/Behavioral/Psychosocial Recommendations**

While there are still many gaps in knowledge and treatment of HIV/AIDS in minority, impoverished, and injection drug-using populations in which HIV-infected women are frequently represented, the following recommendations apply specifically to women.

### ***Transmission Studies and HIV Prevention Needs:***

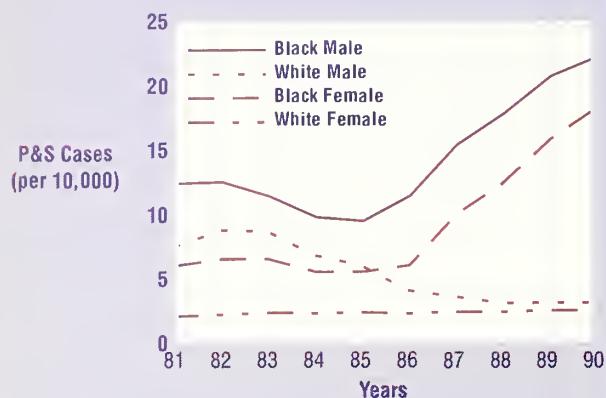
- a. HIV transmission studies (male to female, female to male, female to female) to examine the role of co-infections and other cofactors of transmission (e.g., STDs, age), especially those that may increase transmission via the female genital tract.
- b. Study and develop better barrier/contraceptive methods (e.g., condoms vs. female-controlled methods) and viricides that are effective, safe, and acceptable to women; especially needed are methods that are woman-controlled and may be used without detection by their sexual partners.
- c. Further study behavioral interventions that emphasize the male role in primary prevention of STDs and HIV infection.
- d. Further study the effect of antiretrovirals on transmission factors (e.g., viral load, change in CD4+ counts over time) in pregnant and nonpregnant women.
- e. Improve and expand studies of chemical dependency that underlies HIV risk behavior in women, addressing the following issues:
  - Development of effective therapies and pharmaceutical interventions to treat chemical dependency that do not impair mother-child relationships (e.g., physical separation, incapacitation due to chemical therapeutics).
- Qualitative and quantitative research into all phases of chemical dependency in women, including initiation, habituation, tolerance, and relapse.
- Studies of the relationship between chemical dependency, sexual behavior, and HIV prevention practices of women that employ a multicultural perspective sensitive to the values and beliefs of diverse minority and immigrant populations.
- Evaluation of existing needle exchange and needle disinfection programs for relevance to women.
- f. Further study the seroprevalence and unique HIV prevention needs of subgroups of women (preadolescent and adolescent women; incest and abuse survivors; lesbians; women in prisons, mental institutions, and homeless shelters; disabled women; illiterate and non-English-speaking women).
- g. Develop more specific ethnic identifiers to differentiate between Hispanic and Asian subgroups (to help with community participation, research recruitment, education, etc.).
- h. Evaluate current HIV prevention/behavioral change programs to improve the gender relevance and cultural competence of such programs.
- i. Utilize STD laboratory and clinical infrastructure for HIV/AIDS education and prevention outreach programs.

### ***Progression of HIV Disease in Women:***

Conduct a large-scale cohort study to:

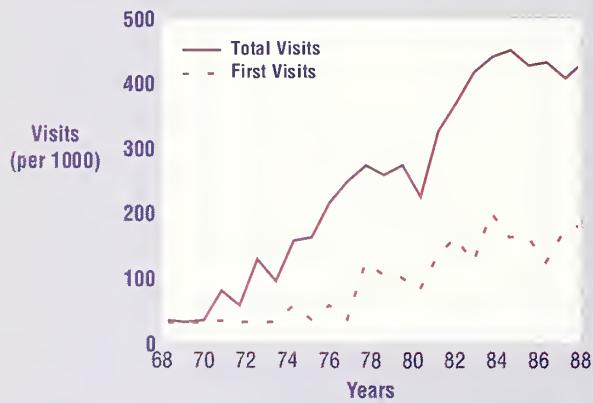
- a. Describe the full spectrum of HIV-related illnesses and malignancies in women to fully evaluate current AIDS case definitions and standards of medical care for women.

**Figure 3.**  
**Primary and Secondary Syphilis by Gender and Race (U.S. 1981-90)\***



Source: MMWR Morb Mortal Wkly Rep 40(19): 314-5, 1991.

**Figure 4.**  
**Genital Herpes Simplex Virus Infections**  
*Number of Visits to Private Physicians' Offices United States, Calendar Years 1966-1989*



Source: IMS America, Ltd.: NOTI

- b. Determine the relationship of immune decline markers (e.g., CD4+ cells) to conditions that may be unique to women (female genital tract and reproductive organ infections) as well as

conditions more common among women (e.g., esophageal candidiasis, bacterial pneumonia).

- c. Study progression of precancerous reproduction organ and genital tract lesions among HIV-infected women (e.g., the interaction of HPV and HIV in carcinogenesis).
- d. Examine relation of survival to such events as AIDS-defining illness or CD4+ cell count to understand factors that contribute to the phenomenon of a shortened survival time for women in comparison to men.
- e. Using culturally appropriate methods, investigate factors that may affect neuropsychological and neurobiological function (including maternal stress factors) and declining immune function.
- f. Study the psychosocial needs of HIV+ women and their family systems' (traditional and non-traditional, including lesbian women) coping with the chronic, crisis-oriented, and usually fatal nature of HIV disease. Give special attention to adolescent psychosocial needs with emphasis on suicide prevention and support strategies.

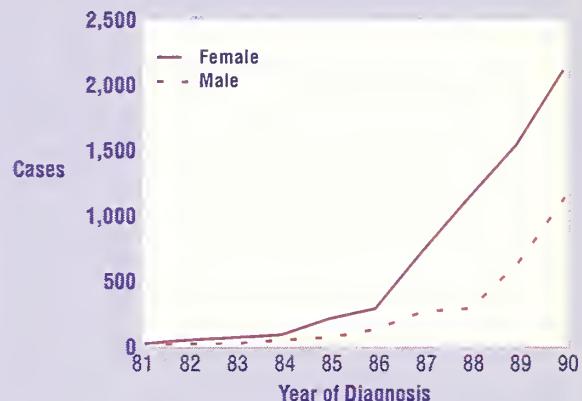
### **Treatment Service and Research Needs:**

- a. Determine the safety and efficacy in women of currently available and experimental HIV therapies, including alternative therapies (e.g., acupuncture). Assess the safety of antiretroviral drugs and therapies for opportunistic infections in pregnant women.
- b. Include gender-specific clinical assessments (e.g., pelvic examinations, Pap smears) as part of the routine evaluation of an HIV-infected woman's medical status; as more is learned of the female-specific manifestations of HIV, new treatments should be developed and tested in a timely manner.
- c. Review clinical trial eligibility criteria in ongoing studies; specifically, inclusion/exclusion

criteria that may be too restrictive and thus prohibit participation of women (e.g., definitions of active drug use, pregnancy, anemia, elevated liver enzymes, etc.).

- d. Evaluate and develop clinical trial recruitment and retention procedures to facilitate enrollment and followup of women (e.g., access to primary medical care, child care, transportation to clinic sites, as well as other support services).
- e. Increase investigations of interactions between HIV therapies and other substances that HIV-infected women may be using (e.g., methadone, oral contraceptives, psychotropic and illicit drugs).
- f. Develop inexpensive, accessible therapeutics that can be used reliably by women who must frequently manage multiple responsibilities (e.g., family, job) despite declining health.
- g. Study the perceptions of women regarding the clinical trial/research process with the aim of developing culturally competent and gender-unbiased education and informed consent procedures.
- h. Improve woman-centered HIV case finding activities with effective counseling (including asymptomatic individuals) in various settings (e.g., prisons, emergency rooms, other institutions) that are directly linked to medical and social services. Employ street and community outreach for HIV case finding.
- i. Determine the extent of health care service needs for HIV-infected women, especially women with multiple medical (including chemical dependency) and psychological diagnoses to improve access, coordination, and quality of care.

**Figure 5.**  
**Cases Among Persons Reporting Heterosexual Contact with Persons with, or at High Risk for, HIV Infection**



Based on cases reported through March 1991 and adjusted for reporting delays.  
Excludes IV-drug users.

- j. Further investigate determinants of health care-seeking behavior in women, including study of the role of social networks/support systems in facilitating women's access to services.
- k. Conduct more research regarding the quality of HIV antibody testing and counseling in women from diverse cultural backgrounds; sexual, addictive, and health behaviors, as well as reproductive and contraceptive choices, should be integral to this process.
- l. Evaluate the adequacy of HIV/AIDS training of health care providers (e.g., Federal training initiatives) particularly as it relates to sensitizing trainees to the needs of women and minorities, including strategies to effectively change biased attitudes toward HIV-infected patients.



## APPENDIX 7



# SUMMARY

## Public Hearing on Recruitment, Retention, Re-Entry, and Advancement of Women in Biomedical Careers



National Institutes of Health  
Office of Research on  
Women's Health (ORWH)

Bethesda, Maryland  
March 2-3, 1992

This document was prepared for  
the Office Research on Women's Health  
National Institutes of Health  
by Computer Management Services, Inc.  
Barbara S. Lynch, Ph.D., Writer

## FOREWORD

The Office of Research on Women's Health was established within the Office of the Director of the National Institutes of Health in September 1990. It was charged with the critical objectives of *giving a central NIH focus to women's health issues and of establishing a science base that will yield reliable diagnoses, effective treatment, and prevention strategies for women.*

Recognizing the actual and potential contribution of women to the advancement of scientific knowledge is a priority for the Office of Research on Women's Health. In addition, we are concerned about (1) providing motivation for the recruitment of women into biomedical careers, (2) the retention of women who have already chosen research careers by assisting them to progress and advance, and (3) the re-entry into the profession by many women who have dropped out of research for a variety of reasons, including the difficulties they faced in combining a research career with their many other roles and responsibilities in life.

The prominence that is currently being afforded women's health issues will, almost certainly, begin to fade unless we can bring about a "critical mass" of women at work in biomedical research. We are convinced that the best means of assuring that research related to women's health remain a visible and active priority as we enter the 21st century is to increase the number of women in policy-making positions in research institutions – including universities, the Federal Government, and the private sector.

It would be naive to suggest that *all* we need to do to remedy the shortcomings in research on women's health is to enlist more women into biomedical research. However, many *are* convinced that there is a direct relationship between the amount – and quality – of research being conducted on women's health issues and the number of women engaged in this research.

We are also concerned about mentors, inspirational support, and opportunities for both traditional and nontraditional pathways for women to be successful in research careers. Our concern extends to the participation of women of all racial and ethnic origins in these endeavors.

We recognize that the attrition rate is alarming for women who enter educational and career paths in science. Even in branches of science where women are well represented at the undergraduate level, their numbers decline at the graduate level, and similar data exist for career progression.

What can be done to bring more women into biomedical research and improve their opportunities for advancement? How can we rectify the loss of women from science education and careers? The Office of Research on Women's Health is looking to the scientific and educational communities to (a) provide us with insight into the major barriers which women face and (b) formulate innovative strategies to overcome those barriers. We seek guidance in how to convince the research establishment of the benefits of having more women participating in research. We plan to address such related issues as tenure, child care and family care, nontraditional pathways to advanced education and careers, problems in the workplace, and new

professional options. Our purpose is to define the necessary "dynamics of change," the solutions and modifications that will alleviate the under-representation of women in scientific professions, and enhance the opportunities for them to assume leadership roles in biomedical careers as we enter the 21st century.

We appreciate the participation of all who have contributed to this process. Your participation affirms that the role of women in biomedical science careers is a deserving priority.

Vivian W. Pinn, M.D.  
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## INTRODUCTION

A Public Hearing was held on March 2 and 3, 1992, on the topic of "Recruitment, Retention, Re-entry, and Advancement of Women in Biomedical Careers." The Hearing was sponsored by the Office of Research on Women's Health (ORWH) and invitations to persons and organizations interested in presenting or submitting testimony were published to the public according to Government protocol.

The purpose of the Hearing was to develop information for planning and conducting a specific activity related to ORWH's three-fold mandate. The mandate of the Office of Research on Women's Health, established in September 1990 within the Office of the Director of the National Institutes of Health (NIH), is the following:

- (1) to strengthen and enhance research related to diseases, disorders, and conditions that affect women and to ensure that research conducted and supported by NIH adequately addresses issues regarding women's health,<sup>1</sup>
- (2) to ensure that women are appropriately represented in biomedical and biobehavioral research studies supported by the NIH, and
- (3) to develop opportunities to increase the participation and advancement of women in biomedical careers.

The activity is a workshop entitled "Women in Biomedical Careers: Dynamics of Change," to be held June 11-12, 1992, in Bethesda, Maryland. The objectives of the workshop are to:

- Generate solid and innovative recommendations for actions
- Develop strategies for enhancing career achievements
- Highlight success stories and programs that work for women
- Provide pathways for networking and collaboration.

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<sup>1</sup>Women's health issues have been defined as diseases, disorders, and conditions that are unique to, more prevalent among, or more serious in women, or for which there are different risk factors or interventions for women than men.

Recently, efforts to attract women to graduate programs and careers in science have yielded positive results, as indicated by their increased enrollment in medical schools and doctoral programs. Yet, women continue to be under-represented in a broad range of scientific professions, especially in leadership positions.

By sponsoring the Public Hearing and workshop on women in biomedical careers, the ORWH sought to identify barriers and obtain a slate of recommendations for action. In addition to guiding the June workshop, these recommendations will enable ORWH and other agencies and organizations to foster efforts to maximize involvement of women in science.

At the Hearing, 43 individuals and organizations presented testimony, and an additional 27 submitted written testimony. This document is a summary of the major issues that emerged during the hearing. Most testimonies described multiple barriers for women pursuing biomedical careers and presented several recommendations for overcoming each barrier. Those hundreds of recommendations tended to group into nine issue areas; thus, this summary is organized according to those nine issues.

For each issue area, the summary presents a synthesis of the relevant barriers, followed by a section highlighting the relevant recommendations. **In some instances, the barriers and recommendations are paraphrased or stated almost verbatim; in other instances a synthesis statement encompasses several similar recommendations, or expands them to be more comprehensive in their application to biomedical careers. For statements in which data are presented, a reference number is printed in brackets { }.** The numbers refer to the numbers of testimony as identified in the appendix of this document. An attempt was made to state each recommendation only once in the summary.

## ISSUES AND RECOMMENDATIONS

### ISSUE 1: Recruiting Women to Biomedical Careers

#### *Barriers*

Although women now constitute the majority of college students, in recent years fewer women students have been enrolling as science majors. Two factors that contribute to this lack of pursuit of science (and math) by women are—

- Discouragement of girls to study science in early grade levels (sex-role stereotyping)
- Failure of career counseling to direct women to the sciences.

***"Girls and women still see science as for 'White Males Only.' "*** {40}

The critical period for encouraging students to enter the sciences is *before* high school. Yet, at each stage in early schooling, girls are culturally and attitudinally discouraged from participating in the physical sciences and mathematics, as is evident from the following facts:

- During grade school, girls are more cognizant of science than boys, but by the time the students reach secondary school, this difference reverses.
- Gender gaps in science show up as early as age 9, and double by age 13. {26}
- During secondary school, girls are not as likely as boys to be encouraged to take math and science courses.
- Beginning in middle and junior high school, girls exhibit more negative attitudes, pursue fewer opportunities, and by the end of high school score considerably lower than boys on measures of mathematics and science achievement, as evidenced by National Assessment of Educational Progress and Scholastic Aptitude Test scores.

- Sex-role stereotyping appears to most seriously affect minority girls, even those who are high achievers.

As a consequence of the lack of exposure and interest, young women are discouraged from pursuing college degrees in science.

Even when young women demonstrate interest and aptitude for science, they are not likely to be directed to a biomedical career by career counselors.

- A questionnaire revealed that students interested in science in high school were discouraged from pursuing a career in science by parents or educators. {48}
- Women are not encouraged in their training to consider *research* careers. Women entering science are often pointed toward and recruited into clinical, administrative, and other direct service roles regardless of demonstrated interest in or aptitude for conducting empirical research.
- Many women, especially ethnic minority women, have difficulty perceiving the advantages and rewards of a research career. Women with specific scientific training continue to be rewarded for their emotional and "people oriented" skills instead of their analytic abilities.

### ***Issue 1 Recommendations***

Early in primary and secondary education young women are both consciously and unconsciously discouraged from pursuing careers in science and math. This, in part, is due to teaching styles that are not sensitive to gender-based differential attitudes regarding capability. Any intervention strategies must increase *both* motivation of students as well as their performance levels, if results in student achievement are going to be effective and long-term. Areas which should be addressed include:

- Teacher education, both pre-service and in-service
- Early childhood education
- Textbooks and instructional material
- Alternative methods of testing and evaluation
- Issues of gender stereotyping, teachers' expectations, and students' self-esteem
- Academic course and career counseling
- Parent education.

More specifically, schools can help negate the myth that girls have no aptitude for science and math by:

- Fostering teacher and student awareness of equity issues
- Creating a climate in which both girls and boys learn mathematical, scientific, and technical skills effectively
- Allocating adequate teaching time to the skill areas in which each gender has the most difficulty
- Providing concrete examples of the usefulness of these skills in future career choices.

The American Association of University Women (AAUW) has recently published a document entitled *How Schools Shortchange Girls* which highlights the need for equity workshops for teachers to help them recognize and address the teaching styles that negatively affect expectations and aspirations of girls and young women. NIH should—

- Join with the AAUW and other organizations in publicizing the result of the studies that form the basis of this document
- Identify and eradicate the ways in which comparable behaviors are perpetuated in educational institutions receiving NIH training grants.

Aggressive programs are needed to direct women into biomedical careers, for example:

- Funding for early identification and motivation programs. Middle schools especially require these types of programs because it is at this level that students begin to consider career goals.
- Local health career high schools or tracks to bring potential students into science and clinical sites to learn skills and to meet successful women scientists.
- More summer programs that allow women high school and undergraduate students to serve as interns in scientific laboratories.
- Mentoring programs in magnet high schools to influence the scientific preparation of women. Such programs would link high school science teachers and students with universities and thereby increase the scientific knowledge and interest of students while improving the quality of high school science programs and teachers.

- Professional linkages between young women in high school and biomedical researchers.
- Summer internships, laboratory tours, seminars, and other programs geared to the high school students, to develop contacts that give a realistic view of research to the students.
- Increased attention and concomitant Federal funding for extramural experiences for undergraduate women students. Participation in these projects, through internships or other work opportunities would offer students another route to developing an interest in science, and would provide contact with adult role models and mentors.
- Financial support to allow postbaccalaureate women to study full-time and finish their courses more quickly.
- Career counseling to expand women's career goals into all areas of biomedical sciences by exposing them through panel discussions and workshops to other women who have made a variety of career choices.
- Research support to allow interested students to work in research laboratories where they become acquainted with hands-on science, have access to mentoring on a one-on-one basis with a research scientist, and receive intellectual and moral support from a network of other students and personnel working in the laboratory.
- Intellectual support through availability of tutors and faculty to aid their progress.
- Intervention workshops for women which focus on such topics as careers in science and how to combine personal and professional lives, among others.

Recruitment efforts of women also should become more aggressive:

- Departmental chairpersons should designate faculty members to coordinate the department's efforts to recruit undergraduate, graduate, and postgraduate students into research careers.
- Administrators of M.D. and Ph.D. programs should identify talented women undergraduates and medical students and actively recruit them.

## ISSUE 2: Visibility: Role Models and Mentors

### *Barriers*

The lack of women role models is a serious barrier to all career phases of women in science: recruitment, retention, re-entry, and advancement. The need to make women in science more visible applies to the general public as well as to specific career aspirants. Seeing predominantly men in high-ranking positions in the biomedical profession subtly reinforces the image that women do not belong in science. If women do not see women successfully balancing career and family responsibilities, they become less able to imagine themselves managing these feats. After a lifetime of negative conditioning, women need the positive one-on-one interactions that mentoring provides in order to remain and advance in science fields.

*"In the 31 science courses I took during my undergraduate studies at the University of Washington, I had two female science professors—both in biology. In medical school, I had five or so female lecturers—but only two full-time professors—out of a faculty of over 100. The opportunity for female professors to serve as role models for the next generation of women is lost for lack of academic appointments."*

- Medical Student

In high school math and science classes, young women describe cultural and sociological barriers and, by graduate school, they report that they often *feel isolated*. There are relatively few women professors, and women students believe that they do not receive the same attention from men teachers as do men students. This is particularly true regarding foreign-born faculty, whose attitudes toward women may be even less egalitarian than that of U.S. men.

In fact, there are few role models for women because of the paucity of women in biomedical career positions, especially in senior faculty and research positions. The table below describes the gap.

*Medical Gender Gap - 1990*

	MEN	WOMEN
Medical School Deans	100%	0%
Physicians	84%	16%
Medical School Faculty	79%	21%
Medical School Students	64%	36%
Nurses	3%	97%

Source: The Feminist Majority Foundation, Washington, DC {62}

A lack of role models implies a lack of mentors, women who can personally guide and encourage other women in their careers. Mentors form a fundamental rung in the career ladder

of medicine. Senior professionals give their junior colleagues attention and feedback, and are a resource for advancement, graduate opportunities, funding projects, and credential support. Without mentoring, women are handicapped in obtaining research grants, publication opportunities, tenure-track positions, and other research and clinical opportunities.

In a 1989 survey of women medical students, 94% reported that they need a mentor, 61% had a mentor, but only 11% have a woman mentor. {1} A survey of the Ruth Jackson Orthopaedic Society reports that only 53% of respondents had a mentor, of which only 16% were women. {13}

### ***Issue 2 Recommendations***

A majority of persons and organizations at the hearing made recommendations for increasing the visibility of women in biomedical careers:

- Encourage women in biomedical careers to *find* mentors and network among organizations.
- Encourage men faculty members to be open to mentoring women students.
- Develop and support mentoring programs at the undergraduate and graduate levels.
- Develop faculty reward systems for 1:1 or 1:2 mentoring of graduate student researchers in the biomedical sciences.
- Develop and publicize a model mentoring program.
- Continue and increase the emphasis on mentoring interested women undergraduate science students and provide the personal contacts into research laboratories to further develop research interests.
- Invite campus scientists to meet informally with women undergraduates.
- Develop symposia on career development which would include discussions on marital choice, children, and family life and their impact on research careers.

- Develop a mechanism for measuring the success of mentoring programs and invest money to make the successful programs more widely available.
- Examine attitudes of women physicians towards their peers. Actively develop women role models in academic medicine and in private practice to help women entering medicine emulate a model different from, but as valid as, the male-dominated tradition of medicine.
- Recruit women researchers into positions where they will be visible and accessible to women in biomedical training.
- Involve women in school curricula, where they can serve as role models for students.
- Showcase the achievements of medical and scientific women, especially women of color, through speakers' bureaus and other publicized efforts aimed at high school, college, and professional audiences.
- Educate chairpersons and training directors about the importance of role models for the career development of all future academics, including women.
- Provide opportunities for networking among women faculty on a national basis to allow them adequate access to role models and mentors.
- Develop programs for the grade-school level that present both women and men as role models in science as well as programs that encourage participation in science through events such as science fairs.

The following recommendations were specifically addressed to NIH:

- Develop mentoring programs and make them available to all principal investigators, covering such issues as how to be a more effective mentor and how to avoid subtle gender bias.
- Improve visibility of women in biomedical research, fund meetings on the subject, support a visiting women lecture series, and increase the number of women on NIH panels.

- Adopt mechanisms for increasing the visibility of women researchers in order to counteract the view widely held not only by girls and young women, but also by their parents, siblings, peers, teachers, and counselors, that scientific research is largely, and properly, a white male endeavor.
- Identify the ways in which NIH, through publications and policies, reinforces the above attitude.
- Provide career guidance to women about the types of assignments and experiences they need for entry into the Senior Executive Service.

## ISSUE 3: Career Paths/Rewards

### *Barriers*

Career paths in the biomedical sciences often do not offer women the same opportunities and rewards they offer men. The statistics verify salary discrepancies between men and women, and the existence of the "glass ceiling." The "Old Boy Network" is still strong, often in the form of male bonding. Women in biomedical careers may have unequal access to appointments, promotion, and tenure, despite their credentials, numbers, or seniority.

*"Our rule of thumb is 'I have to be twice as smart and work three times as hard to get three-fourths the pay and one-half the credit.'" {2}*

Biomedical careers are structured like other fields nationally—with a glass ceiling:

- Only 2% of the Fortune 500's top executives are women.
- No women are in the position of full dean of a medical school.

The two tables below show data on the distribution of medical school faculty. The first table is 1991 data for all departments; the second is 1989 data for departments of pathology.

### Distribution of U.S. Medical School Faculty by Sex, Rank and Tenure Status

TENURE STATUS	PROFESSOR		ASSOCIATE PROFESSOR		ASSISTANT PROFESSOR		INSTRUCTOR	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
Tenured	12,137	1,002	5,500	1,101	459	184	10	10
On Tenure Track	620	72	1,974	428	6,255	2,199	433	316
Not On Tenure Track	2,251	233	4,049	1,032	7,283	3,292	1,985	1,436
Tenure N/A-Clinical Faculty	220	11	245	31	525	138	134	42
Tenure N/A At Institution	660	32	570	77	883	259	278	115
Missing	497	36	722	123	2,347	979	601	419
<b>TOTAL</b>	<b>16,385</b>	<b>1,386</b>	<b>13,060</b>	<b>2,792</b>	<b>17,752</b>	<b>7,051</b>	<b>3,441</b>	<b>2,338</b>

Source: Association of American Medical Colleges, *U.S. Medical School Faculty 1991*, Faculty Roster System, Washington, DC, 1991.

## DISTRIBUTION OF PHYSICIAN FACULTY OF DEPARTMENTS OF PATHOLOGY BY GENDER AND ACADEMIC RANK – 1989

RANK	NO. OF MEN (%)	NO. OF WOMEN (%)	TOTAL (%)
Professor	910 (42.6)	76 (14.3)	986 (37.9)
Associate Professor	551 (25.8)	148 (27.9)	699 (26.2)
Assistant Professor	612 (28.6)	267 (50.3)	879 (32.9)
Instructor	57 (2.7)	37 (7.0)	94 (3.5)
Other and Missing	8 (0.3)	3 (0.6)	11 (0.4)
<b>TOTAL</b>	<b>2,138</b>	<b>531</b>	<b>2,669</b>

Source: U.S. Medical School Faculty: "The Numbers Book" 1989. Faculty Roster System, Association of American Medical Colleges, as presented in R.E. Anderson et al., *Human Pathology*, 22:(no.9):894. {41}

Furthermore, the career path for women not only may lead to a dead-end, but also may be more arduous:

- Men achieve the rank of full professor in 12 years, whereas women labor 20 years to get there. {1}
- Men are four times as likely to achieve full professor rank. {24}

Salary differences exist between men and women scientists:

- In 1986 women scientists earned about 78% of salaries earned by men. The lowest salaries were earned by women in the life and social sciences, 71% and 72%, respectively, of the salaries of men employed in those fields. {26}
- At the doctoral level in 1987, overall women earned 79% of the salaries of men. {26}
- Entry-level salaries appear to be equal, but the disparity in salaries begins around age 30, when men begin to earn more than women. {26}

Nursing scientists have been disproportionately affected by gender-driven stereotyping in their attempts to advance. A common perception is that nurses are not scientists and do not perform studies of scientific merit. Committees have difficulty evaluating proposed studies within the context of the nursing profession.

### *Issue 3 Recommendations*

Participants in the Hearing made the following recommendations:

- Collect data on the career paths of graduates from medical programs.
- Develop a tracking system for the career paths of NIH intramural and extramural scientists (men and women) that monitors promotions.
- Offer incentives, such as equipment or support staff salaries, to universities or departments hiring and promoting women faculty at levels equal to or better than those represented in the pool. It is important to recognize the generational issues involved in funded research today. Many senior faculty, who are predominantly men, came to their positions in a time of generous funding and allocations. It is more difficult today to secure research funding, just at the time that women are making significant inroads into the scientific establishment.
- Offer workshops for departmental chairs to address the issues of (1) how to promote the careers of young faculty, with an emphasis on problems faced by women, and (2) career skills such as writing papers and grant proposals.
- Develop a registry and referral service to better inform research trainees of appropriate employment opportunities and to assist schools and advanced education programs seeking qualified women and minority investigators.
- Investigate, rescind, and/or revise nepotism restrictions and salary limitations in a manner that improves job opportunities for women scientists whose spouses are employed at the same institution. An increasing number of married couples have dual professional careers.
- Acknowledge women without advanced degrees who contribute to successful scientific research.
- Increase the number of women in influential policy positions.
- Increase the number of women in allied health professions on Federal grant review committees.
- Assist women who have entered biomedical careers to advance to leadership positions.

- Conduct a cross-sectional survey of women scientists of all academic ranks, and of those who have left the profession, in order to identify the circumstances that promote or impede the success of women.

"The success of our collective efforts to increase the opportunities and improve access to graduate study and to entry-level research positions in the biomedical sciences will be amplified when there are more women in a position to influence health care and research policy." {7}

- Expand or develop leadership forums and opportunities for women scientists; establish regional forums not only to share information but also to allow women scientists to receive training in leadership skills, business issues, and other areas that will help them develop confidence in skills outside their areas of expertise.

- Offer opportunities to participate in special programs that develop leadership skills, for example:

Leadership training  
Communications skills  
Personnel management  
Assertiveness training  
Stress reduction  
Wellness promotion  
Time management  
Interpersonal relations.

- Offer workshops for professional women specifically aimed at how to effectively use the power of their positions.
- Ensure that women scientists have access to structured professional experiences designed to enhance self-confidence and build independence. This can include opportunities to present and defend research results, evaluate and criticize the research of others, participate in laboratory discussions and decisions, and plan and implement research plans of increasing sophistication.
- Provide a hands-on research experience as part of medical school curricula.
  - Provide opportunities, for residents who wish to have more extensive research training, to elect a research rotation (up to 6 months) or a supervised longitudinal research project integrated into the residency.

- Create linkages with clinical care settings, community-based organizations, and other direct-service providers. As many women, including minority women with interest in research, have opted for direct service and training careers, academic institutions can tap the skills of these individuals by creating collaborative working relationships with these organizations as sources of research subjects and of clinical expertise with special populations.

### *Specially Funded Programs*

- Generate adequate funding for programs that will assure availability of "bridge" research funding to newly trained women beginning their academic careers. These funds would support continued research activity between the training period and the time when new researchers become capable of successful competitive grant funding.
- Make available to women research assistantships and summer research fellowships through foundations, Federal agencies, and medical schools.
- Expand short-term research training grants for pre-doctoral students which afford students research opportunities under faculty preceptorship while they are still in the pre-doctoral program.
- Offer senior fellowships to established women scientists, perhaps made available through a cost-sharing arrangement with participating institutions.
- Design research fellowships to be more flexible; for example, allow for part-time research training.
- Require that institutions demonstrate adequate recruitment and mentoring of women in order to qualify for funding of training programs.
- Establish and fund programs designed to increase research activities by women. These programs could be modeled on NIH's Minority Access to Research Careers (MARC) and Minority Biomedical Research Support (MBRS) Programs, and on the NIMH-funded APA Program for Minority Research Training in Psychiatry and Minority Supplement Awards which provide support for minorities pursuing research training and extra funding to investigators who include a minority co-investigator on their projects.

## **ISSUE 4: Re-entry Into a Biomedical Career**

### ***Barriers***

Many women wish to re-enter biomedical training to continue a career in research or teaching after they have been inactive in the field. These women may have left their careers in order to have and raise a family, or because of financial or geographical reasons. Re-entry may seem to pose overwhelming obstacles and deter women from doing so.

### ***Issue 4 Recommendations***

Programs and funding were recommended for women who wish to retrain or re-enter biomedical careers:

- Make available post-doctoral fellowships for women to retrain or re-enter a field.
- Redesign eligibility rules for fellowships and positions to allow flexibility for accommodating gaps in career activity, for example, regarding the maximum number of years since receiving the Ph.D. or M.D. degree or the number of publications in the prior 5 years.
- Exclude maternity or child-rearing leave from the time limit for tenure decisions.
- Award re-entry fellowships with no stipulation about what school the awardee must attend, thereby allowing women to remain in their homes.
- Offer programs for returning women students whose undergraduate work was not in the sciences, or whose degrees were completed some years ago, who wish to enter research and technical careers. Similar programs already exist for students who wish to pursue a medical degree, but lack the appropriate undergraduate science and mathematics training. Similar programs could be established for those students interested in research-oriented areas.
- Redesign curriculum requirements for individuals taking nontraditional career paths. For example, amend grants to allow time off for child-rearing.

## **ISSUE 5: Family Responsibilities**

### ***Barriers***

The U.S. workforce in 1990 was composed 57.8% of women, 68% of those having children under age 18. If these statistics hold true for women in biomedical careers, one might assume that about two-thirds of the women in biomedical careers have dependents. Unfortunately, the biomedical structure not only fails to accommodate the pregnancy and parenting responsibilities of women, but also unduly penalizes those professional women who choose to have families. Women professionals who wish to bear a child may face disadvantages in planning their career opportunities, and in how they are evaluated for career advancement once they have the child. Women who take time out for pregnancy and child-rearing can lose valuable benefits, forfeit their position on the tenure track, or be harshly judged by medical leaders over the timing and direction of their career path.

Recent surveys indicate the following:

- Nearly 50% of all U.S. medical programs still have no written maternity leave policy. {31}
- Only 37.5% of medical schools have formal maternity leaves. {1}
- 50% of all teaching hospitals have no child care facilities for physicians or staff. {31}
- Only 17% of community hospitals offer child care services. {59}
- Only 18% of medical schools provide child care. {18}

Even when institutions have maternity leave policies, they typically do not resolve scheduling issues posed by dependent care needs:

- Only 14% of residency programs offer part-time or shared residency positions. {59}
- Only 5.5% of medical schools have job-sharing. {1}

*"I wouldn't mind so much the career slowdown that has come with being a mother if that were factored into the mental timetable superiors use when deciding on promotions. A mother's 30-hour week, 10-year career should be compared to a childless scientist's 60-hour week, 5-year rather than 10-year record." {39}*

In an academic career, the time to track tenure and the pressure to be productive occur

early and tend to coincide with prime child-bearing years for women. This factor impedes women's progress into the higher ranks of academic medicine. Women physicians adapt to the needs of the institutions when, instead, the institutions should focus on and provide assistance to the special needs of women physicians.

Thus, balancing family and career is one of the most serious problems facing women who choose biomedical careers. This problem is the most difficult to address because it calls into question both the traditional roles of women in society and the unstated expectations of what it means to be a scientist. The expectation is that in order to be a good scientist, one must be completely devoted to one's work, and in order to be a good mother and partner, one must be completely devoted to one's family.

### *Issue 5 Recommendations*

A majority of persons and organizations giving testimony recommended changes in institutional approach to assessing career progress and accommodating dependent care needs. One organization pointed out that even these measures are not enough if women who take advantage of them are considered "second-rate scientists" who lack dedication. The following recommendations were made:

- The biomedical community should encourage a new definition of "successful career" paths, so that women who have taken time for family responsibilities are not viewed as less committed to their profession, or penalized in their advancement opportunities

#### *Family Leave*

- Distinguish between maternity leave and parental leave and provide for both.
- Formulate formal maternity leave policies for all institutions.
- Formulate maternal leave policies that offer a minimum of 12 weeks family leave.
- Develop work policies which recognize that women still have the major part of child-rearing responsibilities in families. Existing child-care reform and family medical leave packages passed by Congress, could serve as models for what is needed.
- Promote universal acceptance of the need for equitable family leave policies and child care assistance.

#### *Work Schedules*

- Promote the acceptance of and institutionalize flexible-time, part-time positions, and job-sharing opportunities.

- Establish a national clearinghouse of information on such positions in biomedicine.
- Acknowledge the unique needs of women during their undergraduate and graduate medical training, and provide a more flexible schedule and variable graduation dates.

### *Child Care*

- Provide child care facilities at undergraduate, graduate, and post-doctoral institutions.
- Provide child care to women employees at all institutions.
- Provide child-care facilities at convention centers during professional organizational meetings.
- Consider providing stipends for dependent care during training programs.

### *Tenure Track*

- Explore ways to extend or slow the "tenure clock" for those who need to temporarily take time out from their careers for family purposes.
- Develop policies in all institutions to allow delays of the tenure clock to accommodate women with family responsibilities.
- Shift the emphasis placed on publication record from quantity to quality by limiting the number of publications that may be included in applications for promotion or tenure.
- Develop attractive benefits packages in the public and private sectors to include:
  - Health insurance and disability coverage (including pregnancy)
  - On-site child care
  - Maternity leave
  - Set aside funds (grants) structured for researchers in peak child-rearing age
  - Flexible schedules
  - Liberal leave to take care of sick children or sick parents
  - "Work-at-home" assignments
  - Loan forgiveness programs
  - Retirement programs
  - Funding mechanisms for children's college education.

## ISSUE 6: Sex Discrimination and Sexual Harassment

### *Barriers*

For discussion purposes, a distinction is made between sex discrimination and sexual harassment. The former is the exclusion of women from opportunities or unfair assessment of their work because they are women. The latter, sexual harassment, comprises sexual advances in speech or actions. Sex discrimination and sexual harassment both have the same negative impacts on women, society, and the biomedical professions. These impacts were characterized at the hearing as personal, professional, and scientific.

- Personal: The victim's health is affected and the following may result: depression, anxiety disorders, post traumatic stress disorder, psychosomatic illness, gastrointestinal distress, immune suppression, and exacerbated underlying medical conditions. Once such symptoms are present, they are often used by the harassers as "evidence" that the woman deserved the harassment or that she caused it.
- Professional: Science is needlessly impeded by the intentional suppression of the contributions of women scientists by harassers who intentionally bar their victims from completing their scientific work or from gaining recognition for their work.
- Scientific: Who conducts the science affects which questions are considered important and affects how the scientific resources are allocated. It affects which questions are asked and how the questions are framed, which data are collected and how the data are analyzed, as well as how the results are interpreted and applied. Diversity is good for science. It brings a variety of perspectives to bear on solving problems and helps to ensure that the needs of all populations will more likely be recognized and met.

There have been various reports of discrimination and harassment. In a survey by the Orthopaedic Society of its members, 39% of respondents reported sex discrimination during medical school, and 22% sexual harassment; 65% reported discrimination during residency, and 46% harassment. {13} A 1989 survey in Massachusetts revealed that 54% of women physicians and medical students had experienced sex discrimination and 27% harassment in a one-year period. {31}

Last summer, *TIME* magazine reported that women medical students at Stanford University complained of unwanted sexual advances by professors and peers; one student indicated that her breasts had been fondled. {24} In May 1991, the issue received public attention when Frances Conley, neurosurgeon and Stanford professor, resigned for reasons of sexual harassment and the proposed promotion of the fellow surgeon who she felt was treating her in a sexist manner.

Other cited forms of discrimination that undermine morale and productivity are the

following:

- Competent, hard-working, and intelligent women are unfairly characterized as being unfeminine and undesirable.
- Women who do not fall into traditional definitions of "attractiveness," including women of color, are isolated or made to feel invisible to the powers that be.
- Lesbians who are open about their orientation face isolation and harassment.
- Any woman who refuses the advances of men runs the risk of being pushed to "prove" her orientation.
- Women's research is sometimes plagiarized or stolen. In 1988, an AMWA member's research article was stolen by a superior; she was later fired and ostracized for protesting the plagiarism. Although a Federal appeals court supported her plagiarism claim, the male superior has been promoted to a senior position, while the woman researcher is still unemployed. {31}
- Women subordinates often do not receive credit for their contributions. Many principal investigators of research grants are men, but much of the research work is often performed by lower-level, women research assistants; these women are at a significant disadvantage in protesting inequitable treatment.
- Use of forced psychotherapy and forced psychiatric examinations as tools of sexual harassment and as retaliation against women for complaining about harassment is illegal and unethical but all too widespread.
- The dominating style in the scientific workplace is that of men: combative, accompanied by insults and yelling.
- In interviews, women are asked about family plans three times as often as men are asked.

### *Issue 6 Recommendations*

In order to create a professional environment free of gender inequities of any kind, Issues of sex discrimination and sexual harassment must be defined, then confronted through policies at all levels. The following recommendations were made:

- Document the psychological sequelae of discrimination and its impact on employees and institutions.

- Conduct national surveys to document the problem.
- Identify ways in which women can cope effectively.
- Increase nationwide public awareness of the problem through education.
- Require author anonymity in the scientific review process as a means of countering the prejudice against women.
- Develop mechanisms to assure proper credit to research, including a fair hearings appeal process.
- Require medical and graduate school administrators to make clear to students and faculty alike that personal and professional sexism will not be tolerated.
- Develop and enforce sexual harassment policies with prevention and education programs on all campuses.
- Incorporate attitudinal as well as substantive change in curriculum reform regarding gender sensitivity.
- Sensitize faculty and research mentors to the differences in learning and communication styles between men and women.
- Develop arbitration as a possible alternative to lengthy and expensive litigation for tenure appeals and sex discrimination appeals.

*"... snickering, giggling, and generally rude commentary occur any and every time there is a discussion of female reproductive organs."*

*- Medical Student*

*"One woman candidate who thought that her infertility would preclude questions prying into goals regarding family life was nevertheless interrogated regarding possible plans for adoption."*

*- Medical Student*

## **ISSUE 7: Research Initiatives on Women's Health**

### ***Barriers***

The issue was presented of the lack of a medical and research specialty in women's health. Possibly, more women would be attracted to biomedical careers if a specialty focusing on women were available. Even giving more emphasis to women's health in existing programs might attract women to the career field.

### ***Issue 7 Recommendations***

- Emphasize women's health in the education of all health professionals.
- Develop programs specific to women's health in existing health training programs.
- Develop a continuing education program on women's health for physicians in all specialties.
- Offer residency and fellowship programs in women's health.
- Develop a curriculum for a medical specialty in women's health.

## **ISSUE 8: Gender Sensitivity**

### ***Barriers***

Insensitivity to the differences between men and women is a major barrier to compatible working relationships. The style of men tends to be hierachial, noncollaborative, competitive, combative, and noncommunicative.

### ***Issue 8 Recommendations***

The following recommendations were offered as approaches to creating a workplace attitude more compatible to women.

- Offer seminars to men to broaden their scope in the following:

Team Building  
Creative Thinking  
Ethnic Diversity  
Gender Awareness  
Communication Skills

- Foster collaborative and synergistic research
- Promote nonhierachial research teams.

## ISSUE 9: Minority Women in Science

### *Barriers*

All the issues that apply to women in general take on a special intensity for minority women in specific. Barriers to academic achievement, access, equity, excellence in education curricula, academic services, financial assistance, and the scarcity of mentors/role models have kept Hispanics, other minorities, and women from academe.

Given the widespread concern of a glass ceiling for women in biomedical research careers, the predicament for under-represented minority women is so dreary, that for the most part, such a concern is totally abstract. For the overwhelming majority of minority women, careers in biomedical research appear unrealistic and out of reach, let alone worrying about the possibility of a glass ceiling. Although the numbers of minority enrolled in medical schools have increased, and at the same rate as women overall (Association of American Medical Colleges, 1989), the number of minority women in biomedical research careers and medical faculty positions is negligible. {6}

*"For many minority women, to be in a position where a glass ceiling comes into effect would be a drastic improvement." {6}*

A key element to improved health care for minorities is inclusion of researchers who understand the culture, language, and community mores. Yet opportunities for such researchers and research are diminishing. Since 1961, 57 black hospitals have closed, 14 have merged, and only 12 remain. These hospitals are needed for specialized training. {2}

In 1980, the percentage of women physicians in the United States was only 13.4%. Of the total of women physicians, only 0.6% were Hispanic women. The most recent data (1991) for multiple ethnicity groups are presented in the two tables below.

### Distribution of U.S. Medical School Faculty by Sex, Ethnicity and Degree

MALE ETHNICITY	MD NUMBER	PERCENT	PhD/OHD* NUMBER	PERCENT	MD-PhD/MD-OHD* NUMBER	PERCENT	OTHER NUMBER	PERCENT
Native American	37	0.1	7	0.0	2	0.1	1	0.0
Asian	1,942	4.8	1,274	7.1	380	10.5	121	3.0
Black	610	1.5	143	0.8	36	1.0	98	2.4
Mexican American	100	0.2	31	0.2	6	0.2	2	0.0
Puerto Rican	261	0.7	33	0.2	6	0.2	8	0.2
Other Hispanic	603	1.5	121	0.7	64	1.8	35	0.9
White	27,239	67.8	11,444	63.4	2,602	72.1	1,275	31.6
Refused	985	2.5	515	2.9	100	2.8	50	1.2
Missing	877	2.2	278	1.5	45	1.2	341	8.4
<i>Subtotal</i>	<b>32,654</b>	<b>81.3</b>	<b>13,846</b>	<b>76.7</b>	<b>3,241</b>	<b>89.8</b>	<b>1,931</b>	<b>47.8</b>

### Distribution of U.S. Medical School Faculty by Sex, Ethnicity and Degree

FEMALE ETHNICITY	MD NUMBER	PERCENT	PhD/OHD* NUMBER	PERCENT	MD-PhD/MD-OHD* NUMBER	PERCENT	OTHER NUMBER	PERCENT
Native American	5	0.0	7	0.0	1	0.0	4	0.1
Asian	803	2.0	320	1.8	68	1.9	90	2.2
Black	313	0.8	62	0.3	4	0.1	108	2.7
Mexican American	30	0.1	9	0.0	0	0.0	5	0.1
Puerto Rican	116	0.3	22	0.1	0	0.0	15	0.4
Other Hispanic	118	0.3	48	0.3	2	0.1	38	0.9
White	5,545	13.8	3,478	19.3	271	7.5	1,657	41.0
Refused	212	0.5	135	0.7	10	0.3	36	0.9
Missing	351	0.9	122	0.7	13	0.4	153	3.8
<i>Subtotal</i>	<b>7,493</b>	<b>18.7</b>	<b>4,203</b>	<b>23.3</b>	<b>369</b>	<b>10.2</b>	<b>2,106</b>	<b>52.2</b>
<b>TOTAL</b>	<b>40,147</b>	<b>100.0</b>	<b>18,049</b>	<b>100.0</b>	<b>3,610</b>	<b>100.0</b>	<b>4,037</b>	<b>100.0</b>

\*OHD - Other Health Doctorate

Source: Association of American Medical Colleges, *U.S. Medical School Faculty 1991*, Faculty Roster System, Washington, DC, 1991.

Minority women and girls still face race-based stereotypical attitudes, in addition to gender stereotyping. For example, young minority women tend to be neglected or are less likely to be taken seriously in career counseling.

### ***Issue 9 Recommendations***

Special attention to minority women in all programs was recommended, with the following specific suggestions:

- In conducting research, ask different questions to determine race, sex, and socio-economic factors.
- Allocate resources to provide one-to-one, face-to-face recruitment, particularly of minorities, into graduate, science-related programs.
- Provide incentives for schools to develop and retain very diverse student populations (disadvantaged/advantaged, rural/urban, minority/majority).
- Aim research initiatives at minority women's health issues.
- Prepare Asian-American nurses to assume greater responsibility in management positions in health care institutions.

## APPENDIX

### PARTICIPANTS

#### Speakers

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# APPENDIX 8

## *Workshop on Women in Biomedical Careers: Dynamics of Change, Strategies for the 21st Century*

**June 10-12, 1992**  
**Bethesda Marriott**  
**Bethesda, Maryland**

### **Agenda**

#### **Wednesday, June 10**

- 5:30 p.m. Reception With Members of the Congressional Caucus for Women's Issues
- 8:30 p.m. Briefing Meeting for Cochairs, Panelists, and Facilitators

#### **Thursday, June 11**

- 8:00 a.m. Welcome  
Vivian W. Pinn, M.D.  
Director, Office of Research on Women's Health
- 8:15 a.m. Background/History  
Ruth L. Kirschstein, M.D.  
Director, National Institute of General Medical Sciences
- 8:30 a.m. Overview and Workshop Charge  
Task Force Cochairs:  
Carola Eisenberg, M.D.  
Shirley Malcom, Ph.D.
- 8:45 a.m. Panel I: Recruitment, Retention, and Re-entry
- 10:00 a.m. Break

## **Thursday, June 11 (continued)**

10:15 a.m.	NIH Director's Address	<i>Bernadine Healy, M.D. Director, National Institutes of Health</i>
10:45 a.m.	Panel II: Advancement and Workplace Climate	
11:45 a.m.	Panel III: Abuses of Power in the Workplace	
12:45 p.m.	Luncheon	
	Keynote Address	<i>Maxine F. Singer, Ph.D. President, The Carnegie Institution of Washington</i>
2:00 p.m.	Concurrent Strategy Development Sessions	
	<ul style="list-style-type: none"><li>■ Education (Prenatal to 8th Grade)</li><li>■ Education (9th to 12th Grade)</li><li>■ Education (Undergraduate through Doctoral)</li><li>■ Education (Undergraduate through Health Professional Degrees)</li><li>■ Women's Colleges: Their Role in Preparing Women Scientists</li><li>■ Re-entry and Nontraditional Pathways to Success</li><li>■ Workplace Climate: Internal Factors Which Affect Women—Family Issues, Pay Equity</li><li>■ Workplace Climate: External Factors Which Affect Women—Public Images, Stereotypes</li><li>■ Tenure and Promotion</li><li>■ Understanding Power</li><li>■ Harassment in the Workplace</li></ul>	
6:00 p.m.	Meetings of Concurrent Strategy Development Sessions Cochairs and Rapporteurs	

## **Thursday, June 11 (continued)**

- 7:00 p.m. Creative Dinner Discussion Groups
- Networking for Graduate Women in Science
  - The Politics Mother Never Taught You
  - Why Not a Women's Health Specialty?
  - But We've Always Done It Like This: Challenging the Current Structure
  - Science as a Second Language: Ethnic Issues
  - Women Research Themselves: Women Researching Women's Health Issues
  - Building Support Structures—Keeping Your Sanity
  - The "Old Boys Network"—Not for Old Boys Only

## **Friday, June 12**

- 7:30 a.m. Meetings of Concurrent Strategy Development Sessions Cochairs and Rapporteurs
1. Education (Prenatal to 8th Grade)  
Education (9th to 12th Grade)
  2. Education (Undergraduate through Doctoral)  
Education (Undergraduate through Health Professional Degrees)  
Women's Colleges: Their Role in Preparing Women Scientists
  3. Re-entry and Nontraditional Pathways to Success  
Workplace Climate: Internal Factors Which Affect Women—Family Issues, Pay Equity  
Workplace Climate: External Factors Which Affect Women—Public Images, Stereotypes
  4. Tenure and Promotion  
Understanding Power  
Harassment in the Workplace

## **Friday, June 12 (continued)**

- 9:15 a.m.      Exhibition of Innovations:  
Poster/Information Session
- 9:30 a.m.      Creative Dinner Discussion  
Group Reports and Strategy  
Development Session Reports
- 12:30 p.m.      Luncheon
- Address
- Girls, Science, and the Schools:  
What Is Happening, What Needs  
To Happen*
- 1:45 p.m.      Remarks
- 2:00 p.m.      Open Microphone Session
- 3:00 p.m.      Closing Remarks

*Susan McGee Bailey, Ph.D.  
Director, Wellesley College Center for Research on  
Women*

*Antonia C. Novello, M.D.  
Surgeon General, Public Health Service*

# APPENDIX 9

## *Workshop on Women in Biomedical Careers: Dynamics of Change, Strategies for the 21st Century*

**Bethesda Marriott  
Bethesda, Maryland  
June 10-12, 1992**

### **List of Attendees**

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